ORIGINAL ARTICLE

Laboratory-confirmed Congenital Rubella Syndrome at the University Teaching Hospital in Lusaka, Zambia-Case Reports

*** M.L. Mazaba-Liwewe[1,2], A. Mtaja[3], C. Chabala[3], S. Sinyangwe[4], O. Babaniyi[5], M. Monze[2], S. Siziya[6], C. Michelo[7]**

[1]EPI Unit, World Health Organization, Lusaka, Zambia
[2]Virology Unit, University Teaching Hospital, Lusaka, Zambia
[3] Department of Paediatrics and Child Health, University Teaching Hospital, Lusaka, Zambia
[4]Department of Paediatrics and Child Health, School of Medicine, University of Zambia, Lusaka, Zambia
[5]WHO Country Office, World Health Organization, Lusaka, Zambia
[6]Clinical Sciences Department, Copperbelt University, Ndola, Zambia
[7]Department of Public Health, University of Zambia, Lusaka, Zambia

ABSTRACT

Background: Congenital rubella syndrome (CRS) caused by rubella infection in uterine, is a major public health problem among women of child bearing age as it causes serious complications including foetal death or abnormalities including cardiovascular, ophthalmologic, respiratory and hearing impairment. Though there is evidence of rubella infection amongst the population under the expanded programme on immunization (epi) surveillance programme, there is no documented evidence of laboratory confirmed congenital rubella syndrome cases in Zambia. A report is given on four cases of CRS that were identified and confirmed during routine activities of the national measles surveillance program in Zambia. Clinical data on the symptomatic cases were collected and serum samples tested for rubella IgM to confirm the cases.

Case presentation: The first confirmed case was a baby girl presented to the Neonatal Intensive Care unit of the University Teaching Hospital for low birth weight and hypothermia. At seven weeks, the girl was found to have cataracts, spleno-hepatomegaly, microcephaly, and patent ductus arteriosus (PDA). The baby tested positive to rubella IgM antibodies. The second case was a baby boy who was first seen at the University Teaching Hospital at three weeks and on examination was found to have bilateral cataracts, congenital heart disease and microcephaly. Rubella Immunoglobulin M (IgM) results were positive. The third case, a girl, was seen at twelve weeks and brought in for slow growth rate. On examination, the girl was found to have bilateral cataracts, microcephaly and developmental delay. The fourth case is a girl who was brought to the hospital for failure to thrive, tachypnea and fever. On further investigations there was evidence of cataracts, patent ductus arteriosus. At eight weeks, she tested positive for rubella IgM antibodies.

Conclusion: The clinical symptoms and laboratory evidence of rubella infection confirmed congenital rubella syndrome in the four patients. There is an urgent need for surveillance of congenital rubella syndrome and a baseline rubella sero-prevalence survey in Zambia in order to determine the burden of the disease and use this data to direct policy in terms of interventions for supportive treatment, control and possible elimination of rubella infection through immunization with measles-rubella vaccine.

BACKGROUND

Congenital Rubella Syndrome (CRS) is a major public health problem among young women in

***Corresponding author:**
Mazaba-Liwewe M L
Virology Unit, University Teaching Hospital,
Lusaka, Zambia

Keywords: *Congenital Rubella Syndrome; Confirmed; Measles-Rubella vaccine; Lusaka, Zambia*

childbearing age causing serious consequences including miscarriage, foetal death or an infant born with defects [1]. Although an effective vaccine against rubella is available, CRS remains a major public health problem with a total of 121,344 cases reported from 167 countries to World Health Organisation (WHO) in 2009, showing a significant decrease from 67,894 during 2000 in 102 WHO member states. The greatest part of the decrease was in the United States of America and Europe of nearly 100%, followed by the East Mediterranean Region (EMRO) at 35%. All these regions had set elimination goals and introduced a rubella containing vaccine (RCV) routine. In contrast, 20, 14 and 12 fold increases were reported in the African region (AFRO), as well as the South East Asia and Western Pacific regions (SEARO), respectively. In 2009,165 CRS cases were reported from 75 WHO member states globally. [2,3] Studies by Cutts et al. [3] indicating proportions of women susceptible to rubella (sero-negative) in the Africa region report less than 10% in 13, 10-25% in 20 and more than 25% in 12 countries. Zambia is estimated to be in the 10-25%group. Cutts et al. [4] also document that 10% of 20 patients with congenital cataracts and 12% of 34 with congenital heart disease in Tanzania in 1980/81 and 1985/86 had other symptoms compatible with CRS. Zimbabwe recorded 18 cases of CRS in 1978, and 10% of first legal abortions related to rubella infection were reported from South Africa. Tanzania, Senegal and Uganda have also reported occasional cases of CRS [4].

In Zambia, there are no specific programmatic goals relating to the elimination or control of rubella disease and its consequences. The measles surveillance programme, a national case-based surveillance programme running since 2003 and supported by the WHO, has an overall goal to investigate and document the number of children suspected of measles infection under the age of 15 years presenting with fever and rash for measles primarily then rubella. Though there is evidence of rubella infection amongst this population under surveillance, there is no documented evidence of laboratory-confirmed CRS cases in Zambia. Using a model by Miller et al. [5] and data stemming from a study by Watts [6] on rubella antibodies in a sample of Lusaka mothers, Cutts et al. [3] estimated the incidence of CRS to be at 123/100 000 live births in Zambia [5-7].

Early diagnosis of infant rubella infection in CRS cases may allow for the reversal of certain disabilities as well as the disruption of continued virus spreading as it has been documented that children born with rubella infection may continue to shed the virus for even up to one year and hence should be considered infectious. In order to monitor the presence of CRS and control the continued spread of rubella infection, laboratory-backed routine surveillance is a necessity.

This article describes four case reports of CRS that were identified and confirmed during routine activities of the national measles surveillance programme in Zambia. Clinical data on the symptomatic cases were collected and serum samples tested for rubella IgM to confirm the cases.

Documenting the existence of CRS cases is important and emphasizes the need to establish the burden of disease in order to direct policy on control and possible elimination of this devastating condition.

CASE PRESENTATION

We present four confirmed cases of CRS seen at the Teaching Hospital (UTH), Lusaka, Zambia between April 2012 and January 2013. Serological confirmation was performed using rubella–specific IgM (Immunoglobulin M) using ELISA. This was performed using the

Siemens Enzygnost® Anti-Rubella Virus/IgM assay, which is a qualitative and quantitative based immune assay for the determination of specific IgM antibodies to rubella virus in human serum or plasma. To prevent false positives due to rheumatoid factor (RF), pre-treatment with RF absorbent was implemented. The RF also binds specific IgG, thus increasing sensitivity for detection of IgM. The difference in colour intensity/optical density between the antigen well and the control antigen well (? OD) gives the measure of the immunochemical reactivity of the rubella virus specific IgM antibodies in the sample. Any ? OD > 0.2 implies positive acute rubella infection, <0.1 is negative and otherwise is indeterminate. [8]

Case 1

A term low birth weight baby girl was seen and treated in the first week of life for hypothermia and neonatal sepsis. Her birth weight was 1.7 kg and head circumference was 33cm. On physical examination, she was noted to be in mild respiratory distress with a hyperactive precordium, marked tachycardia and a mild systolic murmur in the left sternal border with no hepatomegaly. Initial echocardiographic (ECHO) exam showed; patent ductus arteriosus and peripheral pulmonary stenosis. The mother was a 28 year old, para 2 with unremarkable antenatal history. At seven week, the baby presented with generalised lymphadenopathy, bilateral cataracts, conjunctivitis, tachycardia, hepatomegaly, splenomegaly and head circumference of 34cm. She had gained weight to 2.4 kg. A clinical diagnosis of congenital TORCH infection possibly congenital rubella syndrome was entertained. The diagnosis was confirmed with positive rubella IgM. Rapid Plasma Reagin (RPR) was negative. The child was jointly followed-up by the paediatrics, cardiology and ophthalmology teams.

Further detailed inquiry of the mother antenatal history reviewed that she had a minor rash at six weeks of pregnancy which she 'contracted' from a neighbour's child.

During follow-up, she was treated and discharged for pneumonia and poor growth at 12 weeks. She was notably microcephalic with head circumference 34.5cm(below 5th percentile), weighed 2.34 kg and height 49cm (WHO weight-for-height z score <-2 standard deviation. At 12 weeks clinic review she had a cough, and tachypnoic (respiration rate at 84/minute) and fever (38.6^{o}C) of 3 days duration. Weight at this point was 2.43kg. She had course crepitations bilaterally. On the cardiovascular system, S1 and S2 were heard and noted to be tachycardic but there were no added sounds. Liver and spleen were both still palpable. Bilateral cataracts were also noted. She was readmitted with a diagnosis of Pneumonia/viral pneumonitis secondary to congenital rubella syndrome. She was given Oxygen by nasal cannulae, cefotaxime and cloxacillin, the mother's expressed breast milk, and normal saline nasal drops. Blood was collected for full blood count. The mother was re-counseled and re-interviewed at which point she remembered that she had a rash at six weeks of pregnancy which she 'contracted' from a neighbour's child. The full blood count results were as follows: HB – 11.9g/dl; Platelets – 360,000; White blood count – 23,000; Lymphocytes – 12,280; and Neutrophils – 6,610.

At 7 days post admission, her cough had subsided, probably a response to the treatment. She was breastfeeding well and her general condition was good. Her physical examination revealed a head circumference of 34.5 cm – way below the 5th centile; length 49 cm; weight for length <less than 5th centile; weight 2.6 kg; and heart rate 160/minutes. She was discharged from hospital and the Ophthalmologist booked her for an operation to be done a month later.

Following the confirmation of the above CRS case and sharing of information with clinicians at the pediatrics' departmental meeting, three more cases described below with symptoms and signs suggestive of CRS were identified and investigated.

Case 2

A three week old boy was admitted to the paediatrics ward with bilateral white papillary reflex, congenital heart disease and microcephaly. ECHO showed patent ductus arteriosus. Ophthalmological examination confirmed bilateral cataracts. Serum rubella IgM was positive.

Case 3

A twelve week old girl was brought to the Paediatrics clinic for slow growth rate. On physical examination, the baby though generally active and in good condition, had bilateral cataracts, microcephaly and developmental delay. A serum sample was collected and tested in for rubella IgM. The baby tested positive for rubella IgM.

Case 4

A seven week old baby girl was seen at Paediatrics outpatients' clinic for failure to thrive, fever and difficulty in breathing. She was treated for Pneumonia and Sepsis. Physical examination showed poor growth, and heart murmurs and bilateral cataracts. Further evaluation showed; Patent ductus arteriosus on ECHO, and bilateral cataracts on ophthalmological evaluation. The rubella IgM test was done at 8 weeks and revealed presence of rubella IgM antibodies. At the time of the report, the patient had an appointment scheduled a month later. Discussion

The four cases that we have documented give evidence of congenital rubella syndrome in Zambia. CRS is a neonatal manifestation of intrauterine infection with rubella virus. The signs and symptoms, commonly PDA and cataracts in the cases described in this article along with laboratory confirmation of rubella IgM (indicating active infection) support this evidence. Confirmed CRS is defined as a clinically consistent case whose symptoms include one or more specific signs and symptoms including cataracts or congenital glaucoma, congenital heart disease, hearing impairment, pigmentary retinopathy, purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, or radiolucent bone disease with a laboratory evidence [4, 7, 9-10].

Disease burden associated with Rubella infection has continued to be of great public health concern globally and is still a major and important cause of birth abnormalities. Maternal infection during pregnancy can lead to CRS in the foetus [4, 6]. Identification of 4 cases within a space of nine months in a defined/limited geographic area confirmed circulation of rubella virus in Lusaka. In comparison to the other infections such as Toxoplasmosis, Cytomegalovirus and Herpes in the TORCH infection group, suggests it is an important cause of congenital abnormalities [7, 11-13]. Many children born with CRS will demonstrate persistent neuromotor deficits later in life. Pneumonitis, Diabetes mellitus, thyroid dysfunctions, and progressive panencephalitis are other late expressions of CRS [14-17]. Though the consequences of CRS are devastating and long lasting, supportive treatment can be given especially when detected early. [2, 17-18].

There is scanty information on the evidence of CRS in Zambia or even the prevalence of susceptible women to rubella infection in pregnancy. Watts [6] documented an estimated 12%prevalence of vulnerable mothers in Lusaka. These estimates were used by Cutts and Vynnycky [5] to estimate a CRS incidence

rate of 123/100,000 live births. These statistics were reported more than a decade ago in one demographic area on a limited sample size. Data obtained through the measles surveillance program indicated that 21% of the rash and fever cases investigated were acutely infected with rubella virus in 2011 compared to 2.5% in 2010 [19-20] suggesting an increase in the prevalence of CRS. After literature search, it was established that the four cases that we have reported are the first laboratory-confirmed and documented cases of CRS in Zambia. Since CRS is a rare disease in immunized and non-outbreak communities [17], the incidence rate in Zambia in which vaccination against rubella has not been conducted may be underestimated. The cases described in this paper strongly suggest evidence of rubella virus transmission amongst pregnant women in Zambia. The symptoms observed in three of the four cases, particularly Patent Ductus Arteriosus are suggestive of intra-uterine infection at <20 weeks gestation [6-7, 9]. The observations suggest presence of critical limitations in past and present surveillance efforts.

CONCLUSION

Congenital Rubella Syndrome (CRS) is a major public health problem among young women in childbearing age causing serious consequences including miscarriage, foetal death or an infant born with abnormalities. The clinical symptoms and laboratory evidence of rubella infection confirmed congenital rubella syndrome in our four patients. Although the disease is mild and probably missed, this requires urgent strategic public health responses especially that the effects and defects associated with infection are severe and mostly irreversible in children affected. Though few cases are seen, the devastating consequences in the new-born are long lasting [9]. We suggest testing different interventions, one of which could be the use of a combined Measles-Rubella vaccine (MR vaccine), a vaccine highly recommended by WHO and UNICEF and supported by GAVI [21-22] in national childhood immunization schedules. A clear and well managed immunisation programme is important in ensuring success in control and eliminations of rubella as low vaccination coverage carries the theoretical risk of increasing the occurrence of congenital rubella. [23] There is an urgent need for surveillance of congenital rubella syndrome and a baseline rubella sero-prevalence survey in order to determine the burden of disease and use this data to direct policy in terms of interventions for treatment, control and possible elimination of rubella infection.

CONSENT

Permission was granted by the Ministry of Health after a waiver from the UNZA Biomedical Research Ethics Committee to publish information relating to rubella infection cases confirmed through the national measles surveillance programme. Letter attached.

List of abbreviations

CRS: Congenital rubella Syndrome; WHO: World Health Organisation; EMRO: East Mediterranean Regional; RCV: Rubella Containing Vaccine; AFRO: Africa Region; SEARO: South East Asia and Western Pacific Region; UTH: University Teaching Hospital; OD: Optical Density; NICU: Neonatal Intensive Care Unit; PDA: Patent Ductus Arteriosus; IgM: Immunoglobulin M; RPR: Rapid Plasma Reagin; TORCH: Toxoplasmosis, Others, Rubella, Cytomegalovirus and Herpes; Competing interests

All authors have approved the submission and declare that they have no competing interests.

Authors' contributions

AM, CC, SS[4] made substantial contributions to clinical care. MLML, AM, CC collected the

patient data. MLML, MM, CM interpreted data. MLML drafted the manuscript. MLML, AM, CC, SS, CM, OB, WJM, MM, SS revised and edited the manuscript. All authors read and approved the final manuscript.

Authors' information

MLML: MSc Epi candidate. Department of Community Medicine, School of Medicine, University of Zambia, Lusaka, Zambia. Laboratory scientist. EPI laboratory, Virology Laboratory, University Teaching Hospital, Lusaka, Zambia.

AM: Paediatrics Registrar. School of Medicine. University of Zambia. Registrar. Neonatal unit. University Teaching Hospital.

SS[4]: School of Medicine. University of Zambia. Neonatal unit. University Teaching Hospital.

CC: Paediatrician, Senior Registrar, University Teaching Hospital, Lusaka, Zambia.

OB: WHO representative. WHO country office, Lusaka, Zambia.

WJM: Professor. Department of Epidemiology, International Health & Molecular Microbiology and Immunology. Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA.

MM: Virologist/Head of unit. Virology laboratory, University Teaching Hospital, Lusaka, Zambia.

SS[7]: Professor – Medical Biostatistics. Clinical Sciences Department, Copperbelt University, Ndola, Zambia

CM: Head of department. Department of Community medicine. School of Medicine, University of Zambia, Lusaka, Zambia.

ACKNOWLEDGEMENTS

We acknowledge the contributions of the following individuals and institutions for their contribution to this article:

Ministry of Health – Zambia; University Teaching Hospital (Virology Laboratory); World Health Organisation; EPI National Laboratory team (I Ndumba, T Msiska, J Chibumbya, T Bwalya & E Banda); EPI Surveillance Team (Zambia); Chris Kapp and Medewerkers/Associates for much guidance in the manuscript development; Barbara Otaigbe for the invaluable input; We acknowledge the support provided by the Research Support Centre at the University of Zambia, School of Medicine (UNZA-SoM) through the Southern African Consortium for Research Excellence (SACORE), which is part of the African Institutions Initiative Grant of the Wellcome Trust (company no. 2711000), a charity (no. 210183) registered in England; The National Institutes of Health (NIH) through the Medical Education Partnership Initiative (MEPI) programmatic award No. 1R24TW008873 entitled "Expanding Innovative Multidisciplinary Medical Education in Zambia" at UNZA-SoM; We also acknowledge the various contributions made by the following people for this work: The members of the UNZA-SoM SACORE Steering Committee (Dr Margret Maimbolwa, Dr Paul Kelly, Dr Hellen Ayles, & Dr Charles Michelo) as well as Mr Maxward Katubulushi, Ms Choolwe Nkwemu Jacobs, Ms Mutanti Simonda and Ms Mulemwa Mwangala arranging analytical support.

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