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Clinical manifestations of congenital rubella syndrome at the Korle-Bu Teaching Hospital, Ghana

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Abstract

Background: Congenital rubella syndrome (CRS) is a variable constellation of birth defects related to intrauterine rubella infection which may result in visual, hearing, intellectual and cardiac impairments.

Objective: The objective of this study is to describe the clinical manifestations in patients presenting with CRS at the Korle Bu Teaching Hospital using the World Health Organization criteria**.**

Methods: A retrospective analysis of the medical charts of 16 children under 16 years old who presented with CRS at the Lions International Eye and the National Cardiothoracic Centres of the Korle Bu Teaching Hospital from 2012 to 2015, was done. Ocular, cardiac and other systemic clinical and laboratory findings were documented for each patient using predesigned forms.

Results: Sixteen cases of CRS were recorded over the period (2012-2015) comprising 9 males and 7 females. The median (interquartile range) age at diagnosis was 4.0 months (2.0-7.0 months), age range at diagnosis was 1.0-24.0 months. The main ocular manifestations were; cataract 10 (62.5 %), microcornea 10 (62.5 %), microphthalmia 9 (56.3 %), nystagmus 7 (43.8 %) and strabismus 4 (25.0 %). The main cardiac defects included patent ductus arteriosus 12 (75.0 %), pulmonary stenosis 5 (31.3 %), ventricular septal defect 5 (31.3 %) and small branch pulmonary artery 5 (31.3 %). Systemic conditions recorded included hearing defects 7 (43.8 %), microcephaly 7 (43.8 %), failure to thrive 5 (31.3 %) and mental retardation 2 (12.5 %).

Conclusion: Cataract, microcornea and microphthalmia were the main ocular manifestations in children presenting with CRS at the Korle Bu Teaching Hospital. Patent ductus arteriosus and hearing defects were the main cardiac and systemic defects among children presenting with CRS at the Korle Bu Teaching Hospital.

Keywords: Congenital rubella syndrome, rubella cataract, microphthalmos, patent ductus arteriosus

INTRODUCTION

Congenital rubella syndrome (CRS) refers to variable constellations of birth defects associated with intrauterine rubella infection [1]. It is an important cause of severe birth defects and a public health concern [2]. Women infected with the rubella virus have a 90% chance of passing the virus to their foetus during the early stages of pregnancy, which may result in the death of the foetus or the development of CRS [1]. Rubella is spread in airborne droplets when infected people sneeze or cough. Maternal-foetal transmission of rubella virus occurs via haematogenous spread during maternal viraemia which occurs five to seven days after maternal inoculation [3]. During this period, there are possibilities of a pregnant woman transmitting the virus to her foetus which results in viral infection through the vascular system of the developing foetus [3]. The resulting congenital defects stem from cytopathic damage to blood vessels and ischaemia in affected organs which may eventually lead to birth defects such as ocular, cardiovascular, deafness, and neurological complications among others [4,5]. Foetal infection is chronic and persists throughout gestation and after birth. Typical ocular complications in CRS include cataracts, microcornea, microphthalmia, glaucoma, nystagmus, retinopathy, among others [3, 6]. Cardiovascular defects are reported in 45–50% of children with CRS [6]. These include

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patent ductus arteriosus (PDA), ventricular septal defects, pulmonary artery or valvular stenosis, and secundum atrial septal defect [7, 8]. The CRS is rare in developed countries with established rubella immunization programmes [9]. The CRS however, appears to be endemic in low middle-income areas such as most African countries where little or no rubella immunization coverage exists [10]. From 2000 to 2014, the number of rubella cases reported in Africa increased from 865 cases in seven African countries to 7402 cases in 44 countries. As of 2014, some countries in Africa were yet to introduce routine rubella vaccination programmes [11]. A study by Oduro-Boatey et al. recorded 8 cases of CRS within three months in 1998 at the Child Health Department, of the Korle-Bu Teaching Hospital (KBTH) in Ghana [12]. In August 2013, compulsory rubella vaccination was introduced nationwide in Ghana. However, Ghana is yet to implement a national surveillance system for CRS. Moreover, there is a paucity of published data on the current trend of CRS in the country. Clinically suspicious cases of CRS with associated ocular or cardiac manifestations are occasionally referred to the Lions International Eye Centre and The National Cardiothoracic Centre of the KBTH for further management. With no national rubella surveillance system currently in Ghana, there is a need to objectively investigate and confirm the clinical suspicion and laboratory investigations in cases of CRS. This study reviewed clinical and laboratory findings among patients diagnosed with CRS at the Paediatric Eye Unit of the Lions International Eye Centre and the National Cardiothoracic Centre of the KBTH. It is hoped that the outcome of this study would facilitate the development of effective surveillance for CRS in KBTH specifically, and strengthen the case for a nationwide surveillance system to ameliorate CRS.

MATERIALS AND METHODS

Study design

This was a retrospective descriptive cross-sectional study involving a review of medical charts of children aged less than 16 years and diagnosed with CRS at the Paediatric Eye Unit of the Lions International Eye Centre and The National Cardiothoracic Centre of the KBTH from 2012 to 2015.

Case definitions

Diagnosis of CRS was clinical alone or clinical with laboratory confirmation in some of the cases, using the WHO's definition of CRS [clinically-confirmed CRS was when two of the complications in group 'a' or one from group 'a' and one from group 'b' existed: (a) Cataract(s) and/ or congenital glaucoma, congenital heart disease, loss of hearing, pigmentary retinopathy; and (b) Purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease, jaundice with onset within 24 hours after birth. A laboratory-confirmed CRS case was an infant with a positive blood test for rubella IgM who had clinically confirmed CRS. A positive blood test for rubella IgG suggested previous infection [13]. Failure to thrive was based on weight and height less than the 3rd percentile. Mental retardation was not assessed with IQ tests but was based on microcephaly, i.e. head circumference below 3rd percentile. The roles of toxoplasma, rubella, cytomegalovirus and herpes simplex virus were ruled out through clinical examinations without any specific laboratory tests.

Data collection

Data on systemic history and clinical examinations for each patient such as birth weight, age at presentation, sex, important neonatal problems on patients documented by a paediatrician, antenatal history of the mother such as mothers' date of birth, age at gestation, presence of maculopapular rash and fever during pregnancy, trimester of gestation at maternal illness, and confirmation of rubella in mother were all recorded on a pre-designed case record form. All patients were seen by a paediatrician, paediatric ophthalmologist, an "Ear, Nose and Throat" specialist and a paediatric cardiologist at the KBTH. Visual acuity was assessed using age-appropriate tests including preferential looking tests such as Cardiff cards, or "fixing and following of light". Intraocular pressure measurement was done with the Keeler Pulsair tonometer (Pulsair 2000, by Keeler, Windsor, UK). Anterior examinations were done using a hand-held slit lamp (Zeiss HSO 10, Hand slit lamp and ophthalmoscope illuminator H, Carl Zeiss Meditec AG, Germany) or a pen torch with Volk 20D lens. Posterior segment examinations were done through dilated pupils with an indirect ophthalmoscope (Keeler, UK) and +20D and +28D lenses.

Pupil dilatation was done using a combination of topical Phenylephrine 2.5% and Tropicamide 1%. Ocular ultrasonography (A and B modes) was done using an ultrasound scanner (UD 1000 model, Germany) for axial length measurements and assessment of the posterior segments of the eyes where media was opaque, precluding visualization. Presence or absence of cataracts, congenital glaucoma, aphakic glaucoma, retinopathy, microcornea, microphthalmia, cornea opacification, optic atrophy, strabismus, iris hypoplasia, nystagmus and congenital dacryostenosis were recorded for each patient. Ocular involvement was further classified based on laterality as unilateral or bilateral. All ocular treatments given including surgeries for cataracts and glaucoma as well as anti-glaucoma drugs were also recorded. All the children had detailed systemic examination as well as ear, nose and throat and cardiac evaluations. The cardiac evaluations included a chest radiograph, electrocardiogram and a complete echocardiographic study for the determination of cardiac abnormalities. The echocardiogram which formed the basis of a definitive diagnosis of cardiac abnormalities was performed using a Philips HD15 Echocardiogram 2012, USA. Where necessary patients were sedated with chloral hydrate at a dose of 60 mg/kg stat. All patients with cardiac abnormalities were followed up at regular intervals and medical management was instituted as necessary. Patients requiring surgical interventions had repeat echo-cardiograms done 24 hours to one week prior to surgery.

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Table 1: Ocular manifestations of CRS in patients at the Korle-Bu Teaching Hospital

Ocular signs	Number of patients (%)
Cataracts	10 (62.5)
Microcornea	10 (62.5)
Microphthamia	9 (56.3)
Nystagmus	7 (43.8)
Strabismus	4 (25.0)
Congenital glaucoma	3 (18.8)
Retinopathy	3 (18.8)
Cornea opacification	3 (18.8)
Optic atrophy	1 (6.3)

*Seven (70%) out of the 10 children with cataract had microphthalmia. Nine (90%) out of the 10 cataract cases had microcornea. All three glaucoma cases had cataract and microphthalmia. Ninety percent (90%) of the cataract cases were bilateral. CRS, Congenital Rubella Syndrome.

Table 2: Cardiac manifestations of CRS in patients at the Korle-Bu Teaching Hospital

Cardiac features	Number of patients (%)
Patent Ductus Arteriosus	12 (75.0)
Pulmonary stenosis	5 (31.3)
Branch pulmonary stenosis	2 (12.5)
Small branch pulmonary artery	5 (31.3)
Ventricular septal defect	5 (31.3)
Atrial septal defect	2 (12.5)
Dilated Left Ventricle	1 (6.3)
Tetralogy of Fallot	1 (6.3)

*CRS, Congenital Rubella Syndrome

Table 3: Classification of diagnosis of CRS cases at the Korle-Bu Teaching Hospital

Classification of CRS diagnosis	Num. of patients (%)
Laboratory confirmed (IgM/IgG) with	
Ocular/cardiac manifestations	5 (31.3)
Ocular manifestations only	2 (12.5)
Cardiac manifestations only	2 (12.5)
Clinically confirmed CRS	7 (43.7)

*Num., number; CRS, Congenital Rubella Syndrome; IgG, Immunoglobulin G; IgM, Immunoglobulin M

Laboratory investigations involved serum rubella-specific IgM and IgG. After the collection of blood samples (2 mL), sera were tested by ELISA method using a commercial kit. IgG antibodies were considered positive when the serum level reached 10 U/mL and IgM at 2.5 U/mL. By definition, laboratory-confirmed CRS cases were children who had a positive blood test for rubella-specific IgM, or rubella antibody level that persisted at a higher level and for a longer period than expected from passive transfer of maternal antibody (i.e., rubella titre that did not drop at the expected rate of a twofold dilution per month), usually by 6 months of age. In the conduct of the study, informed consent was not obtained as this was a retrospective study. The study, however, followed ethics regarding the use of patients' clinical data according to the declaration of Helsinki.

Statistical analysis

Data analysis was done using the IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows, Version 23.0. Demographic, laboratory investigations and maternal history of the study participants were presented as mean (standard deviation), median (interquartile range), frequencies and percentages. Presenting ocular, cardiac and systemic manifestations were analyzed and presented as frequencies and percentages. The final classification of CRS was analyzed as laboratory-confirmed CRS positive IgM/IgG with or without ocular, cardiac or characteristic systemic manifestations or both as well as clinical diagnosis with or without IgG positivity.

RESULTS

A total of sixteen cases of CRS were recorded over the period (2012 - 2015) comprising 9 males (56.3%) and 7 females (43.7%). The median (interquartile range) ages at presentation and diagnosis were 2.8 months (2 - 5.8 months) and 4 months (2 - 7 months). The age range at presentation and diagnosis were 0.8 - 24 months and 1 - 24 months. The main ocular manifestations were cataracts (n = 10, 62.5%), microcornea (n = 10, 62.5%), microphthalmia (n = 9, 56.3%), nystagmus (n = 7, 43.8%) and strabismus (n = 4, 25%) (Table 1). Seven out of the 10 children with cataracts had microphthalmia. Nine out of the 10 children with cataracts had microcornea. All 3 patients who had glaucoma had cataracts and microphthalmia. The cataract cases were bilateral in 9 of 10 patients (Table 1). Five of the children with cataracts had surgery with the correction of their aphakia using spectacles. The majority (n = 10, 62.5%) of the patients at presentation could fix and follow light or objects in each eye. Perception of light was elicited in 3 eyes at presentation (Figure 1). A total of 12 (75%) out of the 16 patients had congenital heart diseases. The commonest cardiovascular manifestations were PDA (n = 12, 75%), pulmonary stenosis (n = 5, 31.3%), small branch pulmonary artery (n = 5, 31.3 %) and ventricular septal defect (n = 5, 31.3 %) (Table 2). Other rubella-associated complications recorded were hearing defects (n = 7, 43.8%), microcephaly 9n = 7, 43.8%), failure to thrive

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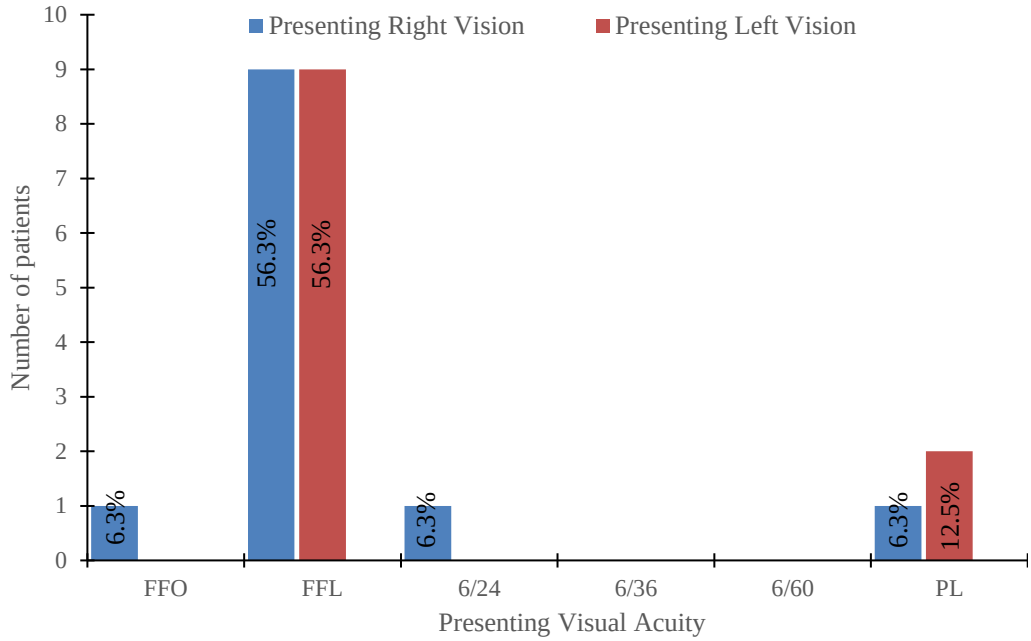

Figure 1: Presenting visual acuity of children with CRS at the Korle Bu Teaching Hospital.
FFO, following objects; FFL, following light; PL, perception of light; RVA, right visual acuity; LVA, left visual acuity

(n = 5, 31.3%) and mental retardation (n = 2, 12.5%). A total of (n = 12, 75%) had multiple conditions. Four (33%) out of the 12 had a combination of cataract, microphthalmia, microcornea, nystagmus, PDA, pulmonary stenosis, hearing defects and microcephaly. Four (33%) out of the 12 had a combination of cataract, micro cornea and PDA. Three (25%) had a combination of cataracts, nystagmus, pulmonary stenosis, hearing defects, microcephaly and failure to thrive. The maternal median age at gestation was 29.5 years (24 - 33.8 years). Maculopapular rash during pregnancy was seen in 2 (12.5%) of the mothers. Two mothers (12.5%) had a febrile illness during pregnancy. Two (12.5%) mothers had the maculopapular rash and fever during the second trimester and one had a fever in the first trimester. None of the mothers reported receiving rubella vaccination. Nine (56.3%) of 16 patients had laboratory confirmation of CRS (IgM and IgG) in addition to ocular or cardiac findings or both. The rest of the patients' (43.7%) diagnoses were clinically confirmed using the WHO definition (Table 3).

DISCUSSION

Congenital Rubella Syndrome remains a significant cause of preventable ocular, cardiac, hearing and neurological morbidities in the paediatric population and a concern for public health practitioners with its attendant social burden [2]. The CRS may affect any organ of the body. However, its burden chiefly results in congenital ocular and cardiac complications with cardiac complications being the most life-threatening defect [7]. The paucity of published data on the current trend of CRS in Ghana makes the findings from this study significant evidence to support literature on CRS in the country. Over these four years (2012-2015), 16 cases of CRS were seen. This may be an underestimation since data from the paediatric department and the ENT clinics of the hospital were not added (due to challenges with the medical records of patients, mostly unavailable or incomplete ocular or cardiac evaluations). In Africa, data on CRS are limited and even the few existing studies on CRS have also reported small numbers of clinically diagnosed CRS cases [10,12-16].

Our series of 16 cases is larger than what was documented by Oduro-Boatey et al. who recorded 8 cases of CRS in 1998 in the Child Health Department of the same tertiary facility for this current study using the WHO guideline for confirmed CRS [12]. Our data for CRS was also higher than the 7 clinically confirmed cases documented in a 5-year series by Otaigbe et al. [15] in a tertiary health facility in Nigeria. These few numbers show that in most developing countries rubella is not a common reportable disease. The condition which is usually mild with subclinical symptoms may even result in misdiagnoses by clinicians [17]. Thus, even with a high index of CRS suspicion, misdiagnosis may occur due to a lack of clear clinical signs of the condition in most mothers and infected babies. Moreover, most developing countries do not have national rubella elimination and surveillance strategies in place to enhance the detection of this under-reported condition. Our findings

show cataract, microcornea and microphthalmia as the major ocular complications associated with CRS. Oduro-Boatey et al. also identified cataracts as the chief ocular complication associated with CRS in Ghana [12]. In another hospital-based study in the Ashanti region of Ghana, all the infants with CRS had cataracts [18]. A global review by Webster mentioned cataracts as one of the complications of CRS affecting 25% of all cases of CRS [5]. According to Givens et al., cataract is one of the significant ocular complications in CRS cases [19]. In another study, cataract was seen as the most common ophthalmic complication mostly occurring unilaterally [20]. In another study in India, paediatric cataract was identified as an ocular complication with high sensitivity for the detection of CRS [21].

The CRS may affect all ocular structures in general, either in isolation or a combination with other ocular complications. In this current study, 70% of the 10 children with cataracts also had microphthalmia and all three cases of glaucoma had cataract and microphthalmia. However, our numbers were not adequate to examine any statistical associations among these conditions though some studies have reported associations between cataracts, microphthalmia and glaucoma [8,19,22]. Other studies have reported that such usual occurrence may not necessarily imply a linkage or an association since microphthalmia is not a specific consequence of congenital rubella but a kind of an ocular failure to thrive. This may be due to the generalized slowing of the replication process associated with rubella infected cells as observed with the concurrent diffused ocular association which results in cataracts and glaucoma in several situations [23-25]. Before the development of the lens capsule in a foetus, the rubella virus may enter the lens resulting in defects at the foetal nuclear stage and subsequent retardation of growth [26]. Cases of congenital glaucoma may be attributed to the failure of absorption of the mesoderm of the angle or the Schlemm canal to differentiate correctly [27]. Though the leakage of proteins from hypermature cataracts may stimulate an increased intraocular pressure, findings from this current study do not explain that glaucoma in microphthalmic eyes may be secondary to lens mediated effects or angle abnormalities.

Since the most rapid development of the heart muscles occurs at the same time as the development of the lens, ocular defects may also be associated with the occurrence of cardiovascular complications [5]. Reported cardiac complications in most CRS cases have justified the need for cardiac examination in all suspected CRS cases [6-8]. In this current study, the main cardiovascular manifestations were PDA, pulmonary stenosis, small branch pulmonary artery and ventricular septal defect. In CRS cases, the incidence of cardiac complications with ocular involvements is known to be as high as 95% [28]. In most cases of CRS, the cardiac complications frequently found are a combination of branch pulmonary artery stenosis and PDA, though the incidence of isolated branch pulmonary artery stenosis may be twice as common as isolated PDA [29]. Lawn et al. [18] reported 6 cases out of 18 cases of CRS involving the heart in Ghana. The outcome of their echocardiography confirmed pulmonary stenosis in 3 of the 6 cases and PDA in 2. Congenital heart diseases were found in 75% of our patients. Other studies reported 85.7% [15] and 40 – 50% [30] from Nigeria. The retrospective design of this study with its inherent limitations, coupled with the small numbers of this rare but important cause of morbidity and mortality in the paediatric age, especially in developing countries where rubella vaccination and surveillance is virtually non-existent, may be limitations. However, this current study has contributed to the documentation of the clinical presentations of CRS in Ghana specifically and Sub-Saharan Africa generally. It may also add to baseline studies conducted in Ghana looking at the clinical profile of CRS, and together serve as the foundation for future surveillance of CRS as Ghana has presently introduced compulsory rubella vaccination since the year 2013. We anticipate a reduction in the prevalence, morbidity and mortality associated with CRS in future.

Conclusion

The main ocular findings from this study were cataracts, microcornea and microphthalmia. Patent ductus arteriosus and hearing defects were the main cardiac and systemic defects among children presenting with CRS at the Korle Bu Teaching Hospital. Early diagnosis, high clinical vigilance for manifestations of CRS and effective surveillance and immunization programmes would help in ameliorating the effect of CRS. A multidisciplinary approach to the management of CRS cases must be encouraged and strengthened with a functioning national surveillance system for CRS. This could help to prevent the occurrence of ocular, cardiac, audiological, neurological and other anomalies associated with CRS with their attendant high morbidity and mortality.

DECLARATIONS

Ethical considerations

The anonymity of study participants was ensured with codes assigned to each patient. All protocols concerning human subjects under the Helsinki Declaration were followed accordingly.

Consent to publish

All authors agreed to the content of the final paper.

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None

Competing Interests

No potential conflict of interest was reported by the authors.

Author contributions

BA**,** VAE, NAY conceived and designed the study, collected data, performed analysis, wrote and reviewed the submitted manuscript. KKO, SM, COB helped to collect data, perform analysis, write and review the submitted manuscript.

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Availability of data

Data is available upon request to the corresponding author.

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