ARTICLE

Ocular manifestations of infants with Congenital Rubella Syndrome (CRS) at Philippine Children's Medical Center from 2015-2021

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OBJECTIVE: The study determined the ocular manifestations as well as the clinico-demographic, maternal profile, and management of infants with Congenital Rubella Syndrome (CRS) seen at the Philippine Children's Medical Center from 2015 to 2021.

MATERIALS AND METHODS: A retrospective chart review was conducted among children less than 1 year of age, born between January 1, 2015, to December 31, 2021, who met the clinical case definition of CRS.

RESULTS: Among the 398 reviewed charts, 312 were suspected cases of CRS, 79 were probable, and 7 were laboratory-confirmed. Ocular conditions were found in 54 suspect cases, 14 probable cases, and 2 confirmed cases. Congenital cataract was the most common ocular manifestation in infants with CRS, and associated clinical manifestations were mainly congenital heart disease followed by microcephaly and hearing loss.

CONCLUSION: This study highlighted the challenge of CRS diagnosis in the country, with most cases diagnosed based on clinical manifestations and a limited number of laboratory-confirmed cases due to the expense and availability of confirmatory tests. These findings emphasize the importance of recognizing ocular manifestations as an early indicator of CRS and the need for improved surveillance and awareness of the disease to facilitate early recognition and management.

KEYWORDS: *Congenital Rubella Syndrome, congenital cataract, rubella infection in pregnancy*

Introduction

Congenital Rubella Syndrome (CRS) is a severe condition resulting from rubella virus infection in non-immune pregnant women, with the greatest risk of congenital infection and defects occurring during the first trimester of pregnancy. CRS can lead to various birth defects, including heart disease, hearing, vision, neurological, endocrinologic, and other disorders [1]. Due to its teratogenic effects, CRS is of significant public health concern. Cases of rubella are underreported in the Philippines, and there is no specific surveillance system for CRS in place. A local retrospective study done by Lopez et al. in 2017 [2] used hospital-based data from four tertiary hospitals, including PCMC, and estimated a national burden of 20 to 31 CRS cases per 100,000 annually, underlining the need for improved monitoring and management.

CRS can cause various ocular manifestations, affecting structures like the lens, retina, ciliary body, and cornea, leading to conditions such as cataracts, microphthalmia, retinopathy, strabismus, and glaucoma [3]. In the Philippines, childhood blindness is a concern, with cataracts being a primary cause [4]. Notably, congenital rubella is identified as a common cause of secondary cataract cases in the country [5], similar to findings in India [6].

This study's objective is to provide data on the ocular conditions of patients suspected or confirmed to have CRS, with a focus on infants seen at the Philippine Children's Medical Center from 2015 to 2021. It also details the clinico-demographic and maternal characteristics as well as the management for the ocular conditions. This is a separate sub-study under the larger multi-center research conducted by Gonzales [7], and the data collected were permitted to be used for analysis in this paper.

Materials and Methods

This descriptive study was conducted with ethics approval from the PCMC Institutional Research - Ethics Committee and employed a retrospective chart review of patients with ocular manifestations associated with CRS.

Patients who were less than 1 year of age and were born between January 1, 2015 to December 31, 2021 were included in the records review. Charts with the following discharge diagnoses were used to identify suspected CRS cases for full review:

Table 1. *Discharge diagnosis with ICD-10 codes for retrieval of charts for review*

Discharge Diagnosis	ICD-10
Congenital rubella syndrome (CRS)	P35
Cataracts (unilateral or bilateral)	Q12.0,
Congenital glaucoma	Q15.0, Q15.9, H40
Pigmentary retinopathy	H35.5
Deafness and hearing impairment	H90

Congenital heart disease	**Q20-Q26**
Patent ductus arteriosus (PDA)	Q25.0
Peripheral pulmonary artery stenosis (PS)	Q25.6
Dermal erythropoiesis	P83.8
Congenital and hereditary thrombocytopenic purpura	D69.42
Microcephaly	Q02
Meningoencephalitis (unspecified)	G04.90
Meningoencephalitis (rubella-associated)	B06.01

The following patients were excluded from review:

Infants <2,500 grams with isolated PDA or isolated microcephaly and no other signs of CRS

Documented negative rubella-specific IgG test for the child

Documented positive laboratory test for other possible etiology of CRS manifestation, such as positive cytomegalovirus or toxoplasmosis test, in the absence of a positive rubella laboratory test

Not a resident of the Philippines

Case Definitions of CRS

Clinical Criteria: an illness, usually manifesting in infancy, resulting from rubella infection in utero and characterized by signs and symptoms from the following:

Category A: congenital cataract/glaucoma, pigmentary retinopathy, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary stenosis), or hearing loss

Category B: purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease

Laboratory Criteria

Isolation of rubella virus,

Demonstration of rubella IgM antibody or infant rubella IgG antibody level that persists at a higher level and for a longer period than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a twofold dilution per month), or

Polymerase Chain Reaction (PCR) positive for rubella virus

Suspect case: A case that has some compatible clinical findings but does not meet the criteria for a probable case.

Probable case: A case that is not laboratory confirmed but has any two conditions listed in category A or one condition from category A and one condition from category B, and lacks evidence of any other etiology.

Confirmed case: A case that has any one condition from category A or one condition from category A and one from category B and meets the laboratory criteria.

Total enumeration of all CRS cases based on the inclusion and exclusion criteria was done. A standardized data abstraction form adapted from the study of Gonzales (2022) [7]

was used for data collection with additional questions on ocular manifestations and interventions done formulated by the primary investigator. Questions on additional ocular conditions, specific surgical interventions, and timing of management were added to the form for this study. The form was converted to an electronic version using the Kobo toolbox platform. Data were collected using the Kobo Collect application using an electronic device either online or offline. Access to the application as well as the encoded data was limited to the investigators and research assistants through standard encryption and password protection. Data collection was done by the primary investigator along with two research assistants.

An initial screening of records was done based on the inclusion and exclusion criteria among infants born between January 1, 2015, to December 31, 2021, with discharge diagnoses as detailed in Table 1. A full chart review was done, and each case was classified based on the case definitions of CRS provided. Those that fulfilled the case definition were classified into suspect, probable, or confirmed cases. Ocular manifestations were recorded, and the clinico-demographic profile, maternal risk factors, and management for the specific ocular conditions were recorded through the Kobo Collect application. Descriptive data analysis was done using Microsoft Excel. Categorical data were expressed as frequency and percentages.

RESULT

In this study, a total of 546 medical records were reviewed, focusing on patients with discharge diagnoses related to Congenital Rubella Syndrome (CRS). After excluding 105 cases and consolidating multiple consults and admissions for the same patient, 398 unique CRS cases were identified. Among these, 312 were suspect cases, 79 were probable cases, and 7 were laboratory-confirmed CRS cases. The analysis showed 54 (13.5%) CRS cases presented with ocular manifestations, highlighting the prevalence of eye-related conditions in infants with CRS. Of the 54, 38 (48.1%) were suspect cases, 14 (17.7%) were probable cases, and 2 (2.9%) were confirmed cases.

Table 2 shows the clinico-demographic profile of CRS cases exhibiting ocular manifestations. The mean age of diagnosis was earlier in laboratory-confirmed cases at 1.2 months (range: 10 days to 2 months) compared to probable cases at an average age of detection at 4.4 months (range: 6 days to 9 months) and suspect cases at 4.7 months. There were more cases among males. Around a third of patients weighed more than 2,000 grams. Due to limitations in chart documentation, more than half of the cases had unknown birthweight. Both confirmed cases tested positive for Rubella IgM, and one was positive for Rubella IgG. Rubella PCR was not requested for any case in this study. All probable and suspect cases were diagnosed based on signs and symptoms and were not serologically tested.

Table 2. *Clinico-demographic profile of CRS cases with ocular manifestations (PCMC, 2015-2021)*

	Confirmed (n=2)	Probable (n=14)	Suspect (n=38)	Total (n=54)
Birthweight				
1,000 to 1,999 grams	1 (50%)	3 (21%)	1 (3%)	5 (9%)
2,000 to 2,999 grams	0	5 (36%)	7 (18%)	12 (22%)
3,000 to 3,999 grams	0	0	6 (16%)	6 (11%)
Birthweight not documented	1 (50%)	6 (43%)	24 (63%)	31 (58%)
Sex				
Male	1 (50%)	8 (57%)	24 (63%)	33 (61%)
Female	1 (50%)	6 (43%)	14 (37%)	21 (39%)
Mean age at CRS diagnosis (mean ± std dev)	1.2 ± 1.2	4.4 ± 3.2	4.7 ± 3.1	4.5 ± 3.1
Age at CRS diagnosis				
1 month and below	1 (50%)	4 (28%)	4 (11%)	9 (17%)
Between 1 to 6 months	1 (50%)	5 (36%)	21 (55%)	27 (50%)
6 months and above	0	5 (36%)	13 (34%)	18 (33%)
Rubella IgM				
Positive	2 (100%)	0	0	2 (4%)
Negative	0	0	0	0
Not done	0	14 (100%)	38 (100%)	52 (96%)
Rubella IgG				
Positive	1 (50%)	0	0	1 (2%)
Negative	0	0	0	0
Not done	1 (50%)	14 (100%)	38 (100%)	53 (98%)

Table 3 illustrates the maternal profile of CRS cases with ocular manifestations. Among confirmed, probable, and suspect cases, the mean maternal age was 27.6 years (range: 18 to 41 years). Around half of the mothers attained at least a high school degree. Majority had prenatal check-ups and delivered in a healthcare facility attended by a healthcare worker. Both confirmed cases had a prenatal history of rubella-like illness while only less than a third of probable cases had a maternal history of fever and rash by recall. Majority of documented maternal rubella-like illness occurred during the first 12 weeks of pregnancy. Half of the suspect cases had unknown history of rubella-like illness. History of exposure to rubella was unknown in most cases (68%).

Table 3. *Maternal profile of CRS cases with ocular manifestations (PCMC, 2015-2021)*

	Confirmed (n=2)	Probable (n=14)	Suspect (n=38)	Total (n=54)
Mean maternal age (in years, mean ± std dev)	23 ± 0	27.4 ± 6.2	27.9 ± 5.2	27.6 ± 5.4
Maternal age				
<17 years old	0	0	0	0
18-29 years old	2 (100%)	9 (63%)	21 (55%)	32 (59%)
30-39 years old	0	2 (14%)	13 (34%)	15 (27%)
>40 years old	0	1 (7%)	1 (3%)	2 (3%)
Unknown	0	2 (14%)	3 (8%)	6 (11%)
Educational attainment				
Elementary graduate	0	1 (7%)	1 (3%)	2 (3%)
High school graduate	1 (50%)	3 (21%)	14 (37%)	18 (34%)
College graduate	1 (50%)	6 (43%)	8 (21%)	15 (27%)
Unknown	0	4 (29%)	15 (39%)	19 (36%)
Prenatal check-ups				
Yes	2 (100)	12 (86%)	32 (84%)	46 (85%)
No	0	0	0	0
Unknown	0	2 (14%)	6 (16%)	8 (15%)
Delivered in a healthcare facility attended by a healthcare worker				
Yes	2 (100%)	11 (79%)	33 (87%)	46 (85%)
No	0	2 (14%)	1 (3%)	3 (6%)
Unknown	0	1 (7%)	4 (10%)	5 (9%)
History of rubella-like illness during pregnancy				
Yes	2 (100%)	4 (29%)	3 (8%)	9 (17%)
No	0	7 (50%)	16 (42%)	23 (43%)
Unknown	0	3 (21%)	19 (50%)	22 (40%)
Age of gestation of rubella-like illness				
12 weeks and below	2 (100%)	4 (29%)	1 (3%)	7 (13%)
13 to 27 weeks	0	0	2 (5%)	2 (4%)
28 to 40 weeks	0	0	0	0
Unknown	0	10 (71%)	35 (92%)	45 (83%)
History of exposure to rubella				
Yes	0	0	1 (3%)	1 (2%)
No	0	5 (36%)	11 (29%)	16 (30%)
Unknown	2 (100%)	9 (64%)	26 (68%)	37 (68%)

Table 4 describes the distribution of ocular manifestations seen in infants with CRS. Some suspect cases presented with more than one ocular finding. Cataract was the most common ocular manifestation in infants with CRS, followed by strabismus and nystagmus.

Table 4. *Ocular manifestations of infants with CRS (PCMC, 2015-2021)*

Ocular manifestations	Confirmed (n=2)	Probable (n=14)	Suspect (n=38)	Total (n=54)
Cataract	0	10	30	40
Strabismus	1	0	5	6
Nystagmus	0	1	4	5
Pigmentary retinopathy	1	2	2	5
Microphthalmia	0	1	1	2
Glaucoma	0	0	1	1
Aniridia	0	0	1	1

In Table 5, the presence of associated systemic conditions in CRS infants with ocular manifestations is illustrated. It was observed that most probable and both confirmed cases exhibited one or more systemic findings, whereas certain suspect cases did not display any associated systemic manifestations. For confirmed cases, microcephaly was the prevailing associated clinical manifestation. On the other hand, among probable and suspect cases, the most observed associated conditions were congenital heart disease, followed by microcephaly and hearing impairment.

Table 5. *Systemic manifestations of CRS cases with ocular conditions (PCMC, 2015-2021)*

Clinical manifestations	Confirmed (n=2)	Probable (n=14)	Suspect (n=38)	Total (n=54)
Congenital heart disease	0	15	8	23
Microcephaly	2	7	2	11
Hearing loss	1	5	0	6
Developmental delay	1	1	2	4
Purpura	0	2	1	3
Neonatal jaundice	1	0	0	2

Table 6 outlines the interventions performed for ocular conditions in infants with CRS. Multiple interventions were done in some cases. In the two confirmed cases, no interventions were carried out for pigmentary retinopathy and strabismus; instead, these conditions were closely monitored through follow-up consultations with ophthalmologists. Nine probable cases and 26 suspect cases had interventions done for their ocular conditions. Among probable and suspect cases with cataracts, lensectomy was the predominant intervention. Remarkably, five of these cases underwent anterior vitrectomy during the same procedure. Additionally, two of these cases also underwent posterior capsulotomy at the same timing as lensectomy and anterior vitrectomy.

Table 6. *Interventions for ocular manifestations of CRS (PCMC, 2015-2021)*

Interventions	Confirmed (n=2)	Probable (n=14)	Suspect (n=38)	Total (n=54)
Lensectomy	0	8	24	32
Medical management	0	1	3	4
Anterior vitrectomy	0	1	5	6
Posterior capsulotomy	0	1	3	4
None	2	5	12	19

Table 7 provides insights into the timing of interventions for ocular conditions in infants with CRS, revealing that approximately one-third of these interventions were initiated when the infants were six months old or younger. However, due to limitations in chart documentation, one-third of cases lacked information regarding the timing of their management.

Table 7. *Timing of interventions performed for ocular conditions in infants with CRS (PCMC, 2015-2021)*

Timing of interventions	Confirmed (n=0)	Probable (n=9)	Suspect (n=26)	Total (n=35)
1 month and below	0	1	2	3
Between 1 to 6 months	0	3	7	10
6 months and above	0	2	7	9
Not documented	0	3	10	13

DISCUSSION

Congenital Rubella Syndrome is an underrecognized public health concern in the country with far-reaching implications. CRS results from maternal rubella virus infection during pregnancy, leading to a wide array of congenital abnormalities and developmental disorders in affected infants. One of the most common manifestations of CRS are distinct ocular findings which may or may not be seen in association with other systemic conditions. The ocular consequences of CRS warrant a focused discussion as they may serve as crucial diagnostic indicators, offering an opportunity to early recognition and intervention.

In the country, cases of rubella remain to be underreported since surveillance is only based on the testing of measles-negative cases. Based on the latest surveillance report by the Department of Health (DOH) Epidemiology Bureau, there was a recorded 541% increase in measles and rubella cases combined from January to February 2023 compared to the same period of 2022 [8]. Similarly, there is also no CRS surveillance in place in the Philippines.

This study identified 38 suspect, 14 probable, and 2 laboratory-confirmed CRS cases with ocular manifestations. Cataract was the most common ocular finding, similar to findings of several local and foreign studies. A retrospective study by Lopez et al. in 2017 showed 52 cataract cases among probable and confirmed CRS cases [2]. A similar study by Vijayalakshmi et al. in 2002 also revealed cataract as the most common ocular finding (93%) with nuclear morphology being the most predominant type [9]. The presence of a nuclear type cataract in a child under 1 year old was revealed to have a 75% positive predictive value for CRS [6] Hence, there should be high suspicion for CRS in any ill infant with congenital cataract.

Another study by Vijayalakshmi et al. in 2007 further exploring the eye signs of congenital rubella showed that the presence of cataract may hold the strongest association with CRS among other eye findings [10]. National congenital cataract data has been used by the several studies as a case finding strategy for Congenital Rubella Syndrome and for extrapolating incidence rates of CRS [2], [11]. Cataract data were well-archived and included the pre-operative assessments, including echocardiograms, which improve documentation of other associated defects.

Pigmentary retinopathy is another common ocular finding in CRS as seen in local [12] and in older foreign studies [13], [14]. Nystagmus and strabismus may also be observed and have been identified in one study as predictors of poor visual outcome [12].

Congenital heart disease was the predominant associated systemic manifestation, which was also observed in

due to difficulty securing clearances from comorbid conditions such as congenital heart disease and acquiring intensive care unit accommodation.

Conclusion and Recommendation

This retrospective study concludes that early recognition of systemic manifestations can facilitate prompt management and improve quality of life. Ocular manifestations may be a useful primary indicator as many of them may be detected at an earlier age compared to other manifestations. The status of CRS in the country is a huge reflection of the effectiveness of existing programs directed at rubella prevention, which is still largely integrated with measles programs. The lack of an established surveillance system needs to be addressed to obtain the true national burden of CRS. New guidelines on CRS surveillance may serve as a good foundation and may be integrated with current rubella programs [20]. This would also promote awareness of the disease and promote early recognition and management.

This study conducted a review of cases of CRS up to 1 year of age presenting with ocular conditions. Future research may explore children beyond 1 year of age to include CRS cases who were diagnosed or sought health consult at a later age, investigate other systemic manifestations of CRS, and examine reasons for delays in management of individual conditions.

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