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CONGENITAL RUBELLA SYNDROME IN EARLY INFANCY: DIAGNOSTIC INSIGHTS AND CLINICAL TRENDS FROM A PAKISTANI COHORT

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ABSTRACT

Background:

Congenital Rubella Syndrome (CRS) remains a significant public health concern in countries with inadequate rubella vaccination coverage. Regardless of global development toward rubella control, limited data are available from Pakistan, specifically concerning the clinical profile and laboratory-confirmed occurrence of CRS in infants. To determine the frequency of laboratory-confirmed CRS among suspected infants and to illustrate the related clinical features at a tertiary care hospital in Karachi, Pakistan.

Methods:

A cross-sectional study was conducted at the Department of Pediatrics, Civil Hospital Karachi on 140 infants under 12 months of age. Suspected infants of having CRS based on clinical criteria, were enrolled using non-probability consecutive sampling. Clinical features including cataract, congenital heart disease, hepatosplenomegaly, jaundice, and microcephaly were recorded. Blood samples were collected and tested for rubella-specific IgM in infants <6 months and IgG in those aged 6–12 months. Data were analysed using SPSS version 21. Frequencies and percentages were calculated, and the Chi-square test was used to determine associations between clinical features and CRS status.

Results:

Out of 140 suspected cases, 54 infants (38.6%) were laboratory-confirmed as CRS positive. Microcephaly (68.5%) and jaundice (72.2%) were significantly more common among CRS-positive infants ($p < 0.001$). Conversely, congenital heart disease (20.4%) and cataract (14.8%) were more prevalent in CRS-negative infants, a finding contrary to expected clinical trends. Pigmentary retinopathy was observed only in CRS-negative cases (5.7%). The differences in clinical presentation suggest the need for comprehensive diagnostic protocols.

	Conclusion: The high occurrence of CRS in this cohort underlines the sustained burden of rubella in Pakistan. Findings emphasize the importance of integrating clinical evaluation with laboratory confirmation for precise diagnosis. Improved rubella vaccination attempts and timely management are desperately required to prevent CRS-related complications and decrease its occurrence in susceptible populations.

INTRODUCTION

Rubella, generally known as German measles, is a communicable disease activated by the rubella virus, usually indicates a mild illness in children and adults [1]. However, its outcomes are distressing when pregnant women get infected, specifically in the first trimester. Intrauterine rubella infection during early pregnancy may cause a spectrum of congenital anomalies collectively termed Congenital Rubella Syndrome (CRS) [2]. CRS is an evitable yet critical condition linked with structural and functional irregularity like sensorineural deafness, cataracts, congenital heart disease, microcephaly, hepatosplenomegaly, and neurodevelopmental disabilities [3-5].

The likelihood of fetal infection is utmost when maternal rubella infection develops inside the first 12 weeks of gestation, with a perinatal transmission rate reaching 90%, and steadily reduces as gestation advances [5-6]. Infants with CRS frequently exhibit with a blend of classic triad symptoms cataracts, congenital heart defects, and deafness along with additional systemic manifestations. In the unavailability of vaccination programs and antenatal screening, rubella stays widespread in many developing countries, conducive to the continued burden of CRS [7].

Despite many developed countries have adequately get rid of indigenous rubella and CRS by extensive use of rubella-containing vaccines (RCVs), low-income countries such as Pakistan still encounter intermittent outbreaks. Pakistan initiated rubella vaccination into its Expanded Programme on Immunization (EPI) in late 2021, one of the last countries in South Asia to do so [8] Before this intervention, rubella immunization treatment was substandard., leaving a considerable segment of women of childbearing age exposed to infection and subsequently expanding the risk of CRS in their children [9-10].

A model-based study by Vynnycky et al. [3] estimated that nearly 32,000 infants were born worldwide with CRS in 2019, with the greatest burden concentrated in the South-East Asia and African regions. The study also highlights those countries without RCV initiation account for over

90% of all CRS cases internationally. A 2020 seroprevalence study executed in Rawalpindi [11], Pakistan, validates this by reporting that approximately 30% of women of reproductive age lacked immunity to rubella, leaving them at constant risk for infection during pregnancy.

Besides creating a health risk, CRS poses substantial economic and social burdens. Each case is associated with lifetime medical care, rehabilitation costs, and social influence on families. A study assessed that the cost of handling a single CRS case in South Asia ranges from $10,000 to $200,000 depending on intensity, comorbidities, and period of care [12].

Routine identification of CRS remains complicated, specifically in settings with low resources. While diagnosis of rubella-specific IgM antibodies in infants <6 months of age is considered a diagnostic marker, serological testing in infants aged 6–12 months depends on sustained rubella-specific IgG without maternal antibodies [13]. In Pakistan, barriers in laboratory infrastructure, inadequate supervision practice, and underestimating further intensify the demand of early CRS detection.

A recent study from Lahore specified a CRS prevalence of 37% among potential cases [14] consistent with global estimates from countries with comparable vaccination gaps. Nevertheless, there is a deficiency of localized data from Sindh province, particularly from high-burden tertiary care centres such as Civil Hospital Karachi, which serves a predominantly low-income population with limited access to prenatal care and vaccinations.

Rationale

CRS continues to be an ignored alarming public health problem in Pakistan, intensified by traditionally minimal vaccination coverage and the delayed incorporation of RCV in the national immunization agenda. While nationwide activities are now initiated to manage rubella, there remains a crucial gap in surveillance data, especially from large public-sector hospitals. This study was proposed to evaluate the frequency of CRS among suspected infants presenting to Civil Hospital Karachi. This study aimed to evaluate how often Congenital Rubella Syndrome (CRS) appears among infants suspected of having the disorder at Civil Hospital Karachi. Comprehending the burden and clinical profile of CRS at this primary tertiary care centre can notify practitioners and regulatory agencies about the requirement for enhanced, rubella screening, maternal vaccination programs, and postnatal management policies.

Objective

To find out the frequency of Congenital Rubella Syndrome in suspected infants presenting to a tertiary care hospital.

Literature Review

CRS is the utmost profound outcome of rubella infection during pregnancy and persists as a major source of avoidable inherited disability globally. According to the Global Burden of Disease study,

CRS occurrence remains elevated in regions without widespread immunization coverage. The study by Vynnycky et al. [3] highlights that more than 100 countries now integrate rubella vaccination in their national schedules. However, 50 countries, comprising parts of South Asia and sub-Saharan Africa still fall behind, leading to the most of fresh CRS cases.

In Pakistan, before the inception of the MR vaccine, rubella susceptibility and maternal infection were often unidentified because of asymptomatic or minor infections. Saeed et al. [11] reported that nearly one-third of women of reproductive age were seronegative for rubella antibodies, underscoring a pressing requirement for catch-up vaccination efforts. Moreover, the 2021 UNICEF national initiative [8] intended to immunize more than 90 million children, but routine vaccination coverage in far off and urban slum areas remains irregular.

Clinical presentations of CRS differ but frequently comprise cardiac irregularities, like patent ductus arteriosus and pulmonary artery stenosis, ocular anomalies such as cataracts and pigmentary retinopathy, and neurological manifestations encompass microcephaly and intellectual disability (15). An international observational study by conducted by Motaze NV et al. [16] reported that ocular and cardiac manifestations were the most common presenting signs of CRS in infants, causing timely identification vital for prompt intervention.

Recent advances in identification, notably enzyme-linked immunosorbent assay (ELISA) and reverse-transcription polymerase chain reaction (RT-PCR), have improved CRS recognition. However, their execution remains restricted in limited resource settings. As Cutts et al. [13] documented that, without further monitoring serological testing, many infants suffering with CRS—particularly those older than six months— may not be detected or miscategorized.

This study extends previous research by aiming on clinical and serological screening of infants under one year of age showing signs of CRS. It intends to produce crucial public health data from Karachi, which can be applicable to reinforce national rubella eradication efforts and enhance maternal-child health outcomes.

Methodology

Study Design and Setting: This was a Cross-sectional study performed at the Department of Paediatrics, Dr. Ruth K.M. Pfau Civil Hospital Karachi. The data collection lasted for six months from June 1, 2019, to December 2, 2019.

Sample Size: OpenEpi version 3.01 was utilized to estimate sample size by using frequency of 37% for CRS among suspected infants, with confidence interval of 95% and absolute precision 5% resulted in the sample size of 140.

Sampling Technique: Non-probability consecutive sampling method was used.

Inclusion Criteria:

- Infants under 12 months of age.
- Both genders were included.
- Infants suspected of congenital rubella syndrome

Exclusion Criteria:

- Refusal to provide informed consent.

- Refusal for laboratory investigations.

Data Collection Procedure: The study was started after getting approval from College of Physicians and Surgeons Pakistan (CPSP), informed consent was obtained from the infant's caregiver. Patients visiting the Department of Paediatrics, Dr Ruth K.M Pfau Civil Hospital Karachi (CHK) meeting the inclusion criteria were registered in the study. A comprehensive clinical history and physical examination were performed. 2–4 ml of blood samples was collected using plain vacutainer tubes and transported to the laboratory. The Serum sample was kept in the refrigerator at -20 degree Celsius. Serum was tested for rubella IgM in infants less than 6 months of age and IgG in infant of age 6-12 months. All pertinent data, together with laboratory results and clinical features were noted by the principal investigator using a structured proforma.

Data Analysis Procedure

SPSS Version 28 was employed to analyse data. Descriptive statistics were used to summarize data as mean ± standard deviation (SD) in case of continuous variables while frequencies and percentages were utilized to summarize categorical variables. Effect modifiers including age and gender were controlled through stratification. After stratification, the Chi-square test was used to evaluate statistical significance. A p-value ≤ 0.05 was considered statistically significant.

Results:

The mean age of participants was 3.21 ± 1.47 months, with the majority of infants (64.3%) aged ≤3 months. Males constituted 54.3% of the sample whereas females accounted for 45.7% (Table 1).

Among the observed clinical characteristics (Table 2) jaundice was the most frequent exists in 52.8% of infants, followed by microcephaly (48.6%), congenital heart disease (39.3%), hepatosplenomegaly (27.9%), and cataract (25.7%). Pigmentary retinopathy was observed in few cases (5.7%).

laboratory verification recognized CRS in 54 infants (38.6%), whereas 86 infants (61.4%) were identified CRS-negative (Table 3).

When comparing clinical features between CRS-positive and CRS-negative infants (Table 4), statistically significant relationship was noticed for numerous features. Microcephaly was observed in 68.5% of CRS-positive infants compared to 36% of CRS-negative infants ($p < 0.001$). Similarly,

jaundice was significantly more frequent in the CRS-positive cases (72.2% vs 38.4%; $p < 0.001$). A substantial segment of CRS-negative infants had congenital heart disease (51.2%) in contrast to only 20.4% in CRS-positive infants ($p < 0.001$. Cataract was significantly more common in CRS-negative infants (32.6%) in comparison to CRS-positive infants (14.8%; $p = 0.019$). Pigmentary retinopathy was documented only in the CRS-negative group (9.3%; $p = 0.021$). There was no evidence of significant relationship between hepatosplenomegaly and CRS status ($p = 0.429$).

Discussion:

In this study, we detected a laboratory-tested CRS prevalence of 38.6% among 140 infants suspected of the condition. This rate is prominently greater as compared to the global average, which observe a 66% decline in CRS occurrence from 2010 to 2019, with nearly 32,000 cases documented in 2019. The raised prevalence in our cohort emphasises the sustained burden of CRS in regions like Pakistan, where rubella immunization coverage has rationally been substandard [3,8 8, 15].

Among the examined clinical features jaundice (52.8%) and microcephaly (48.6%) were the most common. These findings are in accord with the clinical presentation depicted in earlier studies, where jaundice and microcephaly are established manifestations of CRS. Noticeably, microcephaly was significantly more frequent in CRS-positive infants (68.5%) in contrast to CRS-negative infants (36%), emphasizing its distinctive utility [17, 18].

Surprisingly, congenital heart disease (CHD) was noticed in 39.3% of our cases, with a higher occurrence in CRS-negative infants (51.2%) in comparison to CRS-positive infants (20.4%). This contradicts with related studies where CHD is a most common feature among CRS-positive infants. The disparity may be explained due to dissimilarities in study populations or detection criteria [19-21].

Cataracts were observed in 25.7% of our cases, with a higher incidence in CRS-negative infants (32.6%) than in CRS-positive infants (14.8%). This finding is slightly unanticipated, as cataracts are a distinctive feature of CRS. The lower occurrence in CRS-positive infants in our study may indicate inconsistency in clinical presentation or likelihood of mis categorization [15,22,].Pigmentary retinopathy was observed in 5.7% of infants, solely among CRS-negative infants. While pigmentary retinopathy is an established ocular manifestation of CRS, its nonexistence in CRS-positive infants in our study may suggest the difficulties in diagnosis. The inflated occurrence of specific characteristics among CRS-negative infants in our study emphasizes the significance of extensive diagnostic assessments, including laboratory verification, to correctly recognise CRS cases.

Our findings identify the sustained requirement for robust rubella vaccination plans, specifically in localities with high CRS occurrence. The initiation of rubella-containing vaccines (RCVs) has been revealed to substantially alleviate CRS occurrence. Elevated supervision and timely diagnosis are also pivotal in handling and suppressing CRS.

Pigmentary retinopathy was noticeably missing in CRS-positive infants in our study but was present in 9.3% of CRS-negative infants. This is unanticipated result, as pigmentary retinopathy is commonly linked with CRS. Previously studies have noted varied prevalence rates, with few indicating that cataracts are a more frequent ocular manifestation than retinopathy in CRS cases. The nonexistence of pigmentary retinopathy in our CRS-positive cohort may be due to constraint in diagnostic abilities or the schedule of assessments [23-24].

The differences between our findings and those of other studies underscore the need for standardized assessment criteria and complete evaluation frameworks for CRS. Discrepancies in clinical manifestations may also be affected by factors like the timing of maternal infection during pregnancy, genetic vulnerability and access to healthcare facilities [25-26].

Our study reinforces the significance of robust rubella vaccination programs to avoid CRS. The high occurrence of CRS and its related complications in our cohort indicate discontinuity in immunization coverage. Executing extensive vaccination plans, as advocated by the World Health Organization, is decisive to decreasing the incidence of CRS and its burden on affected individuals and healthcare systems.

Conclusion

This study detected a high occurrence (38.6%) of laboratory-confirmed CRS among suspected infants, emphasizing the continuous strain of rubella in Pakistan. Clinical features like microcephaly and jaundice were frequently noticed, whereas unanticipated patterns such as escalated rates of cataracts and CHD in CRS-negative infants indicate diagnostic complexity. These findings underscore the requirement for integrating clinical evaluation and laboratory verification. Increasing routine rubella vaccination and improving timely identification plans are crucial to avoid CRS and its sustained complications. Public health attempts must concentrate on raising responsiveness and coverage of rubella-containing vaccines.

Table 1: Demographic Characteristics of the Study Population (n=140)

Variable	Frequency (n)	Percentage (%)
Age	3.21 ± 1.47	
Age Group		
≤3 months	90	64.3
>3 months	50	35.7
Gender		
Male	76	54.3
Female	64	45.7

Table 2: Clinical Features in Suspected Infants (n=140)

Clinical Feature	Present (n)	Percentage (%)
Cataract	36	25.7
Congenital Heart Disease	55	39.3
Hepatosplenomegaly	39	27.9
Jaundice	74	52.8
Microcephaly	68	48.6
Pigmentary Retinopathy	8	5.7

Table 3: Frequency of Congenital Rubella Syndrome (CRS) (n=140)

CRS Status	Frequency (n)	Percentage (%)
CRS Positive	54	38.6
CRS Negative	86	61.4

Table 4: Association of Clinical Features with CRS

Clinical Feature	CRS Positive (n=54)	CRS Negative (n=86)	P-value
Cataract			
Present	8 (14.8%)	28 (32.6%)	0.019
Absent	46 (85.2%)	58 (67.4%)	
Congenital Heart Disease			
Present	11 (20.4%)	44 (51.2%)	<0.001
Absent	43 (79.6%)	42 (48.8%)	
Hepatosplenomegaly			
Present	13 (24.1%)	26 (30.2%)	0.429
Absent	41 (75.9%)	60 (69.8%)	
Jaundice			
Present	39 (72.2%)	33 (38.4%)	<0.001
Absent	15 (27.8%)	53 (61.6%)	
Microcephaly			
Present	37 (68.5%)	31 (36.0%)	<0.001
Absent	17 (31.5%)	: 55 (64.0%)	

Pigmentary Retinopathy			
Present	0 (0%)	8 (9.3%)	0.021
Absent	54 (100%)	78 (90.7%)	

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