BANGLADESH J CHILD HEALTH 2014; VOL 38 (3) : 137-141

Study of Cardiovascular Malformation in Congenital Rubella Syndrome in Two Tertiary Level Hospitals of Bangladesh

NURE ISHRAT NAZME[1], MANZOOR HUSSAIN[2], MD. MAHBUBUL HOQUE[3], ARJUN CHANDRA DEY[4], ASHITH CHANDRA DAS[5]

Abstract:

Background: *Congenital Rubella infection is a serious disabling problem for children resulting in Congenital Rubella Syndrome (CRS). The exact pattern of the CRS related cardiovascular malformation has not yet been well established in Bangladesh. The objective of this study was to observe the pattern of cardiovascular malformation in Congenital Rubella Syndrome.*

Methodology: *This cross-sectional study was conducted in Dhaka Shishu (Children) Hospital and National Institute of Cardiovascular Diseases (NICVD). Total 40 suspected CRS cases were recruited from both indoor and outpatient departments of the two study hospitals. Serum samples were tested for rubella-specific IgM and IgG, visual and hearing assessment, chest radiography and colour doppler echocardiography were performed at appropriate specialized centres.*

Results: *The mean (±SD) age of the study population (n=40) was 6.6 (±5.7) months (range: 0–24 months), 68% children were male and 32% were female. Congenital heart disease (CHD) was found in 78% children. Patent ductus arteriosus was the commonest (47.5%) structural defect followed by pulmonary stenosis (22%), atrial septal defect (17.5%) and ventricular septal defect (17%). The chest X-ray of CHD cases showed cardiomegaly in 71% cases and patchy opacity and/or consolidation in 65% cases. Regarding serological assessment of the 37 patients (3 patients rejected blood collection), 60% cases showed IgG positive and 28% cases revealed positive IgM.*

Conclusions: *Various forms of cardiovascular malformation are present in CRS patients. Treatment modalities differ in each type of CHD and its early detection can reduce childhood mortality and morbidity.*

Key words: *Cardiovascular malformation, Congenital Rubella Syndrome, Colour doppler echocardiography.*

Introduction:

Rubella is an exanthematous illness characterised by nonspecific signs and symptoms, including transient erythematous rash, post-auricular or suboccipital lymphadenopathy, arthralgia and low grade fever.[1] Maternal infection with rubella during pregnancy, especially in the first trimester results in Congenital Rubella Syndrome (CRS) which is an important cause of blindness, deafness, congenital heart disease and mental retardation.[2] Examination of damaged tissue suggests at least two possible mechanisms for the rubella cytopathology: a direct cytopathic effect, which may involve Rubella virus-induced apoptosis and a virus-induced inhibition of cell division. Vascular injury and resulting insufficiency are more important in the pathogenesis of congenital defects. Non inflammatory necrosis is detected in the endothelial cells within the blood vessels lining the heart and can cause thrombosis of small vessels and necrosis of surrounding tissue.[3]

1. Resident Medical Officer, Dhaka Shishu (Children) Hospital.
2. Professor and head of Paediatric Cardiology, Bangladesh Institute of Child Health, Director, Dhaka Shishu (Children) Hospital.
3. Professor of Neonatology, Bangladesh Institute of Child Health, Dhaka Shishu (Children) Hospital.
4. Assistant Professor, Bangabandhu Sheikh Mujib Medical University, Dhaka.
5. Assistant Professor, Jalalabad Ragib Rabeya Medical College, Sylhet.

Correspondence to: Dr. Nure Ishrat Nazme. E-mail: nazssmc @gmail.com.

The incidence of CRS varies in different populations. According to the World Health Organization (WHO), an estimated 100,000 infants are affected each year worldwide.[4] Incidence of CRS has been reduced in many developed countries by effective vaccination programs. CRS elimination has been resulted in the Americas since 2010. However, rubella vaccination has not yet been introduced in many developing countries. The burden of CRS in these countries is underestimated and few reports documenting the incidence of CRS are available.[5] Incidence of CRS is around 34% in infants of unvaccinated mother and rare in properly vaccinated pregnancies. [5,6]

Annual number of reported rubella cases in Bangladesh was 13,464 in 2009 and 13,125 in 2010.[7] Cardiac abnormalities are classic findings in infants with CRS with approximate incidence 65 per cent.[8] Whether most commonly documented CHD were isolated patent ductus arteriosus (PDA)[9,10] or associated pulmonary artery stenosis (PS),[11,12] other CHD like aortic valvular stenosis, septal defects (ventricular and atrial), transposition of great vessels, tetralogy of fallot (TOF), tricuspid atresia and stenosis of other systemic vessels were also reported.[13]

Thus it is well documented that there is diverse forms of CHD in relation to CRS which is a major cause of mortality as well as lifelong morbidity, if not recognized and treated in early stage.[14] Therefore early recognition of CHD due to CRS and identification of accurate structural heart defects are crucial for paediatricians. There is, however, little detailed information available about the particular types of congenital heart defects that may occur in developing countries like Bangladesh. This study was designed to find out the pattern of congenital cardiac lesions in Bangladeshi children with CRS.

Methodology:

This cross-sectional study was conducted from December 2011 through July 2012. The enrolled patients were the suspected CRS cases of 0-24 months of age who were diagnosed by clinical evaluation according to WHO case definition.[15] The cases were recruited from indoor admissions and cardiac as well as child development center (CDC) outpatient department of the two hospitals- Dhaka Shishu (Children) Hospital and National Institute of Cardiovascular Diseases (NICVD). After taking written consent from parents/ caregivers, a structured case record form was used for data collection. All the children were advised for testing serum rubella-specific IgM and IgG, chest X-ray and colour doppler echocardiography. Visual with hearing assessment were also done from appropriate specialized centres. After 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 at 10 U/ml and IgM at 2.5 U/ml. Laboratory confirmed CRS cases were the 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 titer that did not drop at the expected rate of a twofold dilution per month), usually by 6 months of age.[15] Ethical issues were addressed duly.

Results:

During the study period total 4160 children from both the hospitals were examined and 40 children were suspected as CRS according to the case definition and enrolled in the study. The age range of the study population was 0-24 months (mean 6.6 ±5.7 months) where 53% children were between 0-6 months age group. Male outnumbered female in a ratio of 2:1. Serum antibody against Rubella was advised for all, but parents of 7% cases did not go for investigation. Result was equivocal for IgG in 5% cases. High IgG level (>10 fold of cut-off value) was found in 60% and IgM was found in 28% of study patients (Fig.-1).

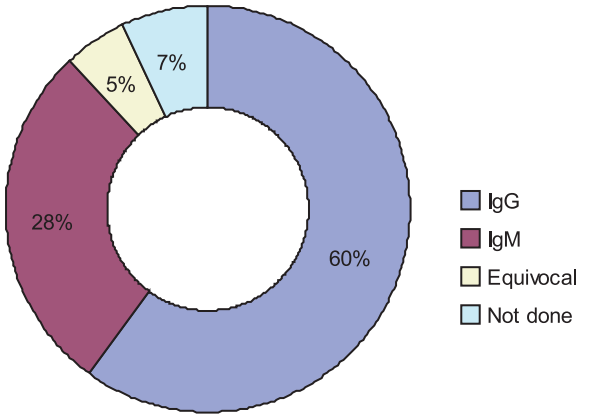

Fig.-1: *Distribution of CRS cases according to serum Immunoglobulin level for Rubella (n=40)*

Among 40 children, 78% had CHD and 22% cases had no CHD (Fig.-2). The chest X-ray of the study patients with CHD (n=31) showed cardiomegaly in 71% cases and patchy opacity and/or consolidation in 65% cases (Fig.-3).

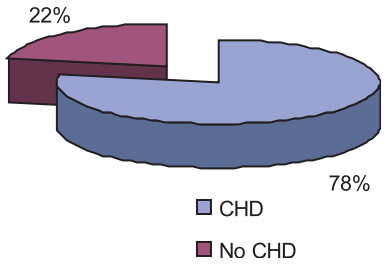

Fig.-2: *Presence of CHD in study patients (n=40)*

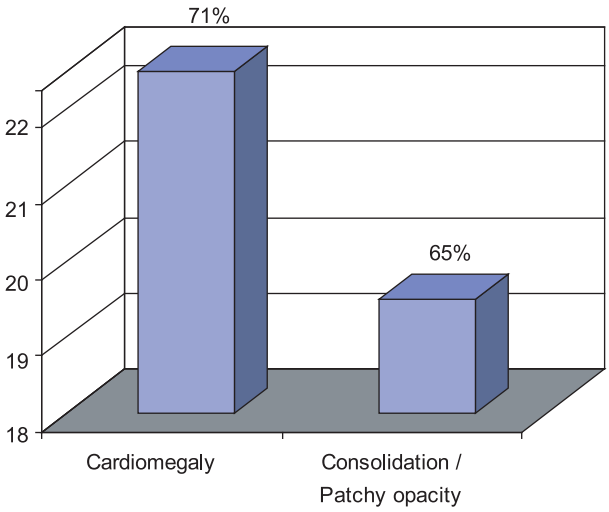

Fig.-3: *Chest X-ray finding of CRS cases in relation to heart disease (n=31)*

The Echocardiography finding revealed PDA in 47.5% children with CRS. Among them 37.5% patients had isolated PDA, 5% had association with ASD, 2.5% with VSD and 2.5% with ASD and TOF. Pulmonary Stenosis was found in 22% cases. Among them isolated PS was found in 10% cases, PS with ASD in 2.5% cases and 10% patients had PS as a component of TOF. ASD was found in total 17.5% cases with isolated ASD in 5% cases and in association with PDA in 5% cases, with PDA and TOF in 2.5% cases, with VSD in 2.5% cases and with PS in 2.5% cases. VSD was present in 17% cases. Among them it was associated with PDA in 2.5% cases, with ASD in 2.5% cases, with truncus arteriosus in 2.5% cases and as a component of TOF in 10% cases (Fig.-4).

Nutritional status of the affected patients was also analysed. Total 93% patients with CHD were malnourished in comparison to 33% patients without CHD. The body weight for age of children with CHD was significantly lower than that of children without CHD (Fig.-5). Chi(X^2) value =4.57, p value- 0.032 (<0.05).

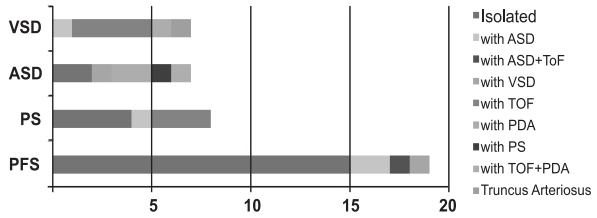

Fig.-4: *Distribution of major CHD in CRS patients (n=40)*

Discussion:

This study was done to see the pattern of structural heart defects associated with Rubella. In this study, most of the patients (53%) were found between 0-6 months of age. Male female ratio was 2:1. It was unclear why male child was predominant in CRS cases, but in many studies the male female ratio of study patients were almost the same.[8, 11]

In this study IgG was regarded positive in most (60%) patients as documented by ten fold rise than upper limit of normal value and 28% patients revealed positive IgM. Although WHO, CDC and many other authors recommended confirmation of CRS by detection of rubella specific IgM in blood and persistence of rubella IgG titres over time, i.e., no decline in titre as expected for transplacentally derived maternal IgG (by 6 months),[16] IgM is more specific serological test than IgG and confirmation of the diagnosis based solely on the presence of rubella IgG is difficult.[17] Rubella specific IgM can be detected in almost 100% of infected infants of 0-3 months of age.[18] However, The percentage of IgM positive infants progressively declines over the first year of life (less than 50%), until at 1 year most infants are negative. But IgM may not be detected until at least 1 month of age. This could be the consequence of the fact that congenital infected neonates have high Rubella specific IgG titers of both self and maternal origin that tend to compete with IgM antibodies for binding.[18] In this study, all the IgM positive children were within 0-3 months of age.

In a study from south India, 26% children were seropositive for rubella IgM which was consistent with this study (28%). Therefore, even more specific for confirmation, serum IgM estimation alone may under-diagnose CRS compared to combination of both the

tests (IgM and IgG) [19] and Rubella-specific IgG test is more practical for diagnosing CRS in children aged > 6 months. For many reasons, including laboratory capabilities and cost issues, IgM and IgG testing for rubella infection are more likely to be available in developing countries like ours.[20] In 7% cases, serum was difficult to obtain, due to parental refusal and result was equivocal for IgG in 5% cases. They could be potential cases of laboratory confirmed CRS if retested later to see rising antibody titre. But all of them were included as clinically confirmed CRS cases according to WHO guideline.[15]

Incidence of CHD varies in different studies. In an active surveillance for Congenital Rubella Syndrome in Yangon, Myanmar CHD was the most common sign of CRS (72%) [20] which is more consistent with this study. A Spanish study also found strong association of CHD with perinatal infection by Rubella Virus.[21]

Regarding pattern of CHD patent ductus arterisus was documented as the predominant congenital heart disease by several authors, followed by pulmonary stenosis.[9-11] It was consistent with this study. PS and septal defects were also commonly associated with PDA in different studies.[12] However, a wide variety of cardiac problems, associated with CRS was documented by other authors like- TOF, transposition of the great vessels, dextrocardia, tricuspid atresia, coarctation of the aorta, myocarditis, ebstein anomly, aortic regurgitation and eisenmenger complex.[12,22] Pattern of cardiac problems were also diverse in this study. Here PDA was found in most (47.5%) children with CRS followed by PS, ASD and VSD. In addition to isolated defects there were combined forms of cardiac defects.

The chest X-ray of the study patients with CHD (n=31) showed cardiomegaly in 71% (22) cases and patchy opacity and/or consolidation in 65% (20) cases. CHD is a very common cause of pneumonia, especially recurrent pneumonia, as described by some authors.[23] Again in an autopsy study in Ghana, CHD was found as an important cause of cardiomegaly.[24]

Conclusions:

Cardiovascular malformation is one of the major abnormalities associated with CRS which increases childhood morbidity and mortality. Cardiac defects appear in multidimensional ways ranging from mild to severe and isolated to combined defects. So the paediatricians should be aware of early detection of CHD in relation with CRS.

Limitation of the study:

A limitation of this study is the relatively small sample size, which limited the detection of many other structural heart defects. Here all children were included as clinically confirmed CRS cases and more laboratory confirmed CRS cases could be discovered if sera were retested for antibody.

Recommendations:

Paediatric Cardiology is a flourishing paediatric specialty in our context. Therefore, all suspected CRS cases must be evaluated by colour doppler echocardiography to detect structural heart defects. Women who are planning or becoming pregnant should be vaccinated at least 28 days before that to reduce the incidence of CRS and its serious sequels. National surveillance must be boosted up for extensive research on pre-vaccine and post-vaccine status of children. The WHO recommends that all countries that have not yet introduced rubella vaccine should consider its inclusion in their national immunisation programme.[5]

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