

CONGENITAL HEARING IMPAIRMENT ASSOCIATED WITH RUBELLA: LESSONS FROM BANGLADESH

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Abstract. Infection with rubella virus during pregnancy may cause fetal death or the multiple congenital fetal abnormalities that are known as congenital rubella syndrome (CRS). Studies have demonstrated that congenital hearing impairment is the most frequent abnormality associated with intrauterine rubella infection. In the present study, the first of its kind in Bangladesh, we investigated the presence of rubella antibody in hearing-impaired children in order to understand the possible role of rubella infection in the development of hearing impairment. A total of 198 hearing-impaired children and 200 children without hearing problems were studied. After taking a detailed history from the parents, blood samples were collected from both mothers and children; sera were subjected to enzyme-linked immunosorbent assay (ELISA) for anti-rubella IgG. Rubella antibody was detected in 74% of the hearing-impaired children and in 18% of those with normal hearing: this finding correlated with the presence of rubella antibody in the mothers (67%) of rubella seropositive hearing-impaired children. In contrast, we observed rubella antibody in only 14% of the mothers of the children without hearing problems. Consistent with the presence of antibody, 41% of the seropositive mothers who had hearing-impaired children gave a history of fever and rash during early pregnancy. Our study indicates a strong association between rubella infection and hearing impairment in Bangladeshi children. In addition, it also indicates that infection by rubella virus is common in Bangladesh: this suggests that priority should be given to implementing appropriate measures for the control of rubella.

INTRODUCTION

Rubella virus is an enveloped single-stranded RNA virus that belongs to the genus *Rubivirus* of the *Togaviridae* family. Only one type of rubella virus is described and humans are the only known host (Cooper, 1985; WHO, 2000). Infection with this virus causes an exanthematous illness characterized by non-specific signs and symptoms including a transient erythematous rash that be pruritic, low-grade fever, arthralgia and lymphadenopathy (Centers for Disease Control and Prevention, 1998).

Rubella infection is highly contagious and is transmitted by droplets. Before the introduction of the vaccine, rubella was endemic in many countries. Epidemics were superimposed on the endemic infection every 6 to 9 years in the United States and every 4 to 5 years in Europe (Centers for Disease Control and Prevention, 1998). The major public health importance of rubella infection relates to the teratogenic effects of primary rubella infection in pregnant women (Gregg, 1941; South and Sever, 1985). The stage of pregnancy at which the disease is developed appears to be of crucial importance. Infection in the early months of pregnancy may result in the multiple congenital fetal abnormalities that are known as the congenital rubella syndrome (CRS).

The worldwide pandemic of rubella infection between 1962 and 1965 highlighted the

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importance of CRS; more than 20,000 cases of CRS were reported to have occurred in the United States alone (Orenstein *et al*, 1985). In developing countries, the burden of CRS has been assessed and it has been found that during rubella outbreaks, rates of CRS per 1,000 live births can be as high as 1.5 (Singapore), 0.7 (Oman) and 0.9 (Sri Lanka) (Cutts *et al*, 1997). Rubella surveillance data from developing countries show that epidemics occur every 4-7 years: somewhat similar to the situation in Europe during the pre-vaccination era. In most populations, unless there is a mass immunization program, around 10% of women are still susceptible to rubella when they reach child-bearing age (Centers for Disease Control and Prevention, 1998).

The abnormalities most commonly associated with CRS include sensorineural deafness, cardiac defects (PDA, ASD, VSD), visual impairment (*eg*, cataracts) and CNS pathology (*eg*, microcephaly, mental retardation). In addition, infants with CRS frequently exhibit both intrauterine and postnatal growth retardation. CRS has been estimated to occur among 20-25% of infants born to women who acquire rubella during the first 20 weeks of pregnancy (Centers for Disease Control and Prevention, 1998).

Hearing impairment, either alone or in combination with other defects, is the commonest abnormality associated with rubella babies (Cooper, 1975). Studies of children with congenital hearing loss have suggested that the contribution of congenital rubella may be higher than suspected on the basis of clinical studies only. In Finland, a serological survey of 128 infants aged 6 months to 5 years with moderate or severe congenital hearing loss revealed the presence of rubella-specific antibody in 45% of those studied (Ojala *et al*, 1973). It was also reported that 74% of children with congenital deafness in Trinidad had rubella antibody (Karmody, 1968). Congenital hearing impairment may occur following maternal infection up to the nineteenth week of pregnancy (Cutts *et al*, 1997). There are several studies which indicate that hearing impairment is severest

when rubella infection occurs in the second month of gestation; this impairment is sensorineural (Goodhill, 1950; Barr and Lundstrom, 1961; Anderson *et al*, 1970).

Although rubella infection in pregnancy is considered to play a critical role in the development of congenital hearing impairment, and several studies have revealed a high risk of CRS in developing countries, there is no precise information available on the prevalence of rubella infection, or on the association of this infection with congenital hearing impairment, in Bangladesh. In this case-control study, we investigated the presence of rubella antibody among children with congenital hearing impairment and compared the findings with those of healthy children. The aim of the study was an understanding of the association of rubella with the development of congenital hearing impairment in Bangladeshi children. This is the first study to demonstrate a relationship between rubella antibody and congenital hearing impairment in Bangladesh.

PATIENTS AND METHODS

The subjects enrolled in this study were hearing-impaired children from the Society for Assistance for Hearing Impaired Children (SAHIC), a specialized center for hearing and speech defects, and children with normal hearing from two conventional primary schools located in Dhaka. The study was approved by the Research Board of National Diagnostic Network and was conducted during 1998-1999. One hundred and ninety-eight children from SAHIC were studied. The inclusion criteria for this case group were: a) age below 10 years; b) a history of hearing impairment since the first year of life; c) a diagnosis of sensorineural deafness. All the children in this group were diagnosed as having sensorineural deafness by the otorhinolaryngologists working at SAHIC, whose judgment was supported by thorough audiometry. We excluded patients who had been admitted to the center because of delayed speech development but whose hearing ability was found to be normal in the

course of rehabilitation. The control group (N=200) were from conventional primary schools; the inclusion criteria were: a) age below 10 years; b) no degree of hearing impairment. Only after having obtained the written consent of the parents were the children enrolled in the study.

After taking a detailed history from the parents, blood samples were collected from both mothers and children; these samples were transported quickly to the Central Laboratory of National Diagnostic Network (NDN) and the sera were subjected to enzyme-linked immunosorbent assay (ELISA) using a commercial ELISA kit (*Sorin*, Biomedica, Italy) in order to determine the level of anti-rubella IgG. The tests were carried out according to the manufacturer's instructions. Appropriate negative and positive control were used: IgG antibodies were considered positive when the serum level reached ≥ 10 IU/ml.

RESULTS

A total of 146 of the 198 subjects (74%) suffering from hearing defects were found to be positive for anti-rubella IgG (Table 1). Most of the positive cases were between 5~10 years of age (89%). By sex, the prevalence rate was similar: male 76%; female 71%. In contrast, of the 200 children having no hearing problems, anti-rubella antibody was detected in only 36 children (18%). There was no significant difference in prevalence between males and females (Table 2).

We then investigated the rubella antibody levels of the mothers of all the rubella seropositive children (both those with hearing impairment and the controls). Of the 146 mothers of deaf rubella-seropositive children, 98 were found to have anti-rubella antibodies - a preva-

Table 1
Presence of anti-rubella IgG antibody in children suffering from sensorineural hearing impairment.

	Anti-rubella IgG positive		
	N	N	(%)
Overall	198	146	(74)
1~4 years	66	28	(42)
5~10 years	132	118	(89)
Male	107	81	(76)
1~4 years	38	19	(50)
5~10 years	69	63	(91)
Female	91	65	(71)
1~4 years	28	9	(32)
5~10 years	63	55	(87)

Table 2
Presence of anti-rubella IgG antibody in the control children.

	Anti-rubella IgG positive		
	N	N	(%)
Overall (Age:5~10yrs)	200	36	(18)
Male	100	20	(20)
Female	100	16	(16)

Table 3
Presence of anti-rubella IgG antibody in the mothers of seropositive children.

	Anti-rubella IgG antibody		
	N	N	(%)
Mothers of hearing impaired children	146	98	67
Mothers of normal children	36	5	14
Total	182	103	57

Table 4
History of fever with rash in the mothers of hearing impaired and normal children
(by trimester).

	Fever with rash				%
	1 st tri	2 nd tri	3 rd tri	Total	
Mothers of hearing impaired children					
Seropositive (98)	24	16	0	40	41
Seronegative (48)	2	0	2	4	8
Mothers of normal children					
Seropositive (5)	0	1	0	1	20
Seronegative (31)	0	0	0	0	0

Figures in parentheses denote the number of subjects.

Table 5
History of other illness in rubella seropositive normal and hearing-impaired subjects.

Group	Mumps	Measles	Ear discharge	Meningitis
Impaired hearing				
Rubella seropositive (146)	0	6	4	6
Rubella seronegative (52)	0	2	4	2
Normal hearing				
Rubella seropositive (70)	2	4	6	4
Rubella seronegative (130)	0	4	4	4

Figures in parentheses represent the number of subjects.

lence rate of 67% in the mothers of affected children (Table 3). Of the 36 mothers of seropositive children with no hearing problems, 5 (14%) were found to be seropositive. Of the 98 seropositive mothers of hearing impaired children, 24 and 16 gave a history of fever and rash in the first and second trimester of pregnancy respectively (Table 4). In addition, 8% of the rubella seronegative mothers of hearing-impaired children also gave a history of fever and rash during pregnancy; only one of the seropositive mothers of children without hearing impairment gave a history of fever and rash (second trimester).

We also recorded the history of other illness in rubella seropositive normal and hearing-impaired children (Table 5). Among the hearing-impaired rubella seropositive chil-

dren there was a history of measles (6 cases), ear discharge (4 cases) and meningitis (6 cases). Almost the same medical history was given by the children with no hearing problem, the only exception being two children who had a history of mumps.

DISCUSSION

Rubella is found the world over and is normally considered to be a harmless viral disease of childhood. Nevertheless, infection during early pregnancy may cause fetal death or CRS. CRS is an important cause of hearing impairment in countries where rubella infection has not been controlled or eliminated. Although the burden of CRS is not well

characterized in all countries, it is estimated that more than 100,000 cases of CRS occur every year in developing countries alone (WHO, 2000). In countries where rubella vaccination has not been introduced, periods of low rubella activity alternate with epidemic waves at intervals of 4-8 years. During rubella epidemics the incidence rates of CRS may increase from approximately 0.1-0.2 to 1-4 per 1,000 live births without a marked difference between developed and developing countries (WHO, 2000). During the United States' epidemic in the early 1960s, before rubella vaccination, 12.5 million cases were reported including 20,000 cases of CRS. The congenital damage resulted in over 11,000 deaf and 3,580 blind children and more than 1,800 children with mental retardation.

In spite of its worldwide prevalence, there had been no reports of either the clinical or serological prevalence of rubella in Bangladesh. This seems to be due to the fact that rubella was not considered to be a major health problem by the Bangladeshi medical community. We found a strong association between rubella infection and hearing impairment; in addition, this study indicated a high incidence of rubella infection in children suffering from hearing problems as well as in those having no such problems. As far as we are aware, this is the first evidence of the relationship between rubella infection and sensorineural hearing impairment in Bangladesh.

Infection with rubella virus has several teratogenic effects in pregnant women. After infection in the first trimester, there is an approximately 50% increased risk of spontaneous abortion (Siegel *et al*, 1966). CRS manifestations in surviving infants may include permanent structural defects like deafness, cataracts and congenital heart disease. Sensorineural deafness is the commonest defect resulting from intrauterine infection with rubella (Gumpel, 1972); it is usually bilateral but can be unilateral (Sheridan, 1964). The fetus is believed to be infected transplacentally as a result of maternal viremia developing after a primary infection in pregnancy (Hanshaw and

Dudgeon, 1978). Gestational age is considered to be critical factor in determining the degree of fetal damage following infection (Majeed-Saidan, 1983). If the infection occurs before 8 weeks of pregnancy, then the fetus will be severely affected, ranging from miscarriage or stillbirth to an infant with CRS. Infection after 8 weeks may not be that severe and an apparently normal infant may be born.

Antibodies in response to rubella are first detectable about 14-18 days after infection, at about the time the maculopapular rash appears. A rise in anti-rubella IgM and anti-rubella IgG levels is observed, although IgM levels decrease fairly rapidly, and by about 8 weeks are usually undetectable; the IgG persists (Vesikari, 1972; WHO, 2000). In the present study, anti-rubella IgG was detected in 74% of the severely hearing impaired children and in 18% of the children having no hearing problem. These results indicate that infection by rubella virus is not uncommon in Bangladesh and that there is a good correlation between the serology and the hearing impairment. The results of this study are consistent with those of several other studies (Gumpel *et al*, 1971; Ojala *et al*, 1973; Zakzouk and Al-Muhaimeed, 1996) and further confirm the role of this virus as an important etiological factor in the development of sensorineural hearing loss.

The presence of antibody in the children correlated well with the presence of antibody in the mother and also with the maternal history of rash and fever during early pregnancy. Among the mothers of the seropositive hearing-impaired children, 67% were found to be rubella seropositive; of these seropositive mothers, 41% gave a history of fever and rash during pregnancy. This finding is in keeping with the results of Gumpel *et al* (1971) who found that 25% of cases were without a maternal history.

We also recorded the history of other illnesses in both normal and hearing impaired children but failed to observe any significant association between hearing loss and any other illness. This observation supports the notion that rubella plays a critical role in the development of hearing impairment.

We observed a strong association between rubella infection and hearing impairment. Control measures must be taken to control and prevent rubella in Bangladesh. In many developed and some developing countries, large scale rubella vaccination during the past decade has drastically reduced rubella and CRS. Rubella vaccines are highly protective and without significant side-effects. All the cost-benefit studies of rubella vaccination, in developing and developed countries, have found firmly in favor of the rubella vaccination, which is economically justified, especially when combined with measles vaccine (WHO, 2000). Based on the present global burden of CRS, the World Health Organization (2000) recommended that all countries assess their rubella situation and, if appropriate, make plans for the introduction of rubella vaccination. In addition to the requirements for the surveillance of any vaccine-preventable disease, there are additional needs that are specific for rubella because of its impact on pregnant women. For countries wishing to prevent the occurrence of CRS, the WHO has recommended that rubella vaccination, as part of a national immunization program, should be offered to all children at the age of 12-18 months. The addition of rubella vaccination to the measles vaccination program, using combined measles and rubella vaccines, is strongly encouraged where affordable. However, as the elimination of CRS based on childhood vaccination alone requires at least 20-30 years of continued commitment, ideally, all susceptible, non-pregnant women of child-bearing age should receive the rubella vaccine until childhood vaccination has resulted in full adult protection.

For any country to arrive at a rational decision regarding the choice of vaccination strategy, regular and representative surveys to assess the susceptibility to rubella infection amongst young women should be given high priority. In addition, appropriate other methods for CRS surveillance include clinical reports, hospital records, studies on rubella and deaf/blinds, and active searches for CRS cases after outbreaks of rubella.

The high infection rate in the children having no hearing problem also indicates a high prevalence of rubella infection. Although several developing countries have already introduced this vaccine to their routine immunization program, Bangladesh has not, and may therefore be at risk of an epidemic like that seen in Sri Lanka (Gunasekera and Gunasekera, 1996). The present study sends an important message regarding the assessment, control and prevention of rubella infection in Bangladesh.

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