EXTENDED REPORT

Prevalence of eye signs in congenital rubella syndrome in South India: A role for population screening

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Purpose: Congenital rubella syndrome (CRS) resulting from maternal rubella infection, especially in the first trimester, affects an estimated 100 000 infants each year worldwide. Immunisation has reduced its occurrence in the developed world, though it remains a problem in countries with poor immunisation coverage. This population-based study was aimed at screening children below 5 years of age for ocular signs suspicious of CRS.

Methods: Suspected CRS cases were recruited from hospital and outreach services of the Aravind Eye Care System over a 24-month period. Clinical confirmation was based on the fulfilment of the World Health Organization (WHO) definition, and laboratory confirmation was based on a positive test for IgM antibody.

Results: Children under 5 years of age (n = 51 548) with ocular complaints were screened for eye signs suspicious of CRS; CRS compatible signs were detected in 1.92% (1090) children. Of these suspects (299), 27.42% were subsequently confirmed clinically according to WHO definition, and (46) 4.2% were serologically (Laboratory) confirmed. Of all the eye signs evaluated for screening, cataracts were the most sensitive (80.43%).

Conclusions: Cataracts among children have a high sensitivity for detecting CRS in India. It is the only clinical eye finding that has a high enough sensitivity and specificity to be useful as a screening tool for CRS.

Maternal infection with rubella in the first trimester of pregnancy results in congenital rubella syndrome (CRS). This is an important cause of blindness, deafness, congenital heart disease and mental retardation.[1] An estimated 100 000 infants are affected each year worldwide.[2]

Rubella vaccine is not included in the immunisation schedule in India, and there is no routine surveillance for rubella infection or CRS. According to recent reports from India, a significant proportion of women of child-bearing age are susceptible to rubella infection.[3]

Several hospital-based studies have shown 10–15% of congenital cataract in infants is due to maternal rubella in India,[4–8] but the criteria to be used for screening rubella suspect are unresolved.[9]

This population-based study was aimed at screening children below 5 years of age with ocular signs suspicious of CRS, confirming the presence of rubella through clinical examination and serological assays.

METHODS

Suspected cases of CRS among children 0–59 months of age were recruited from the routine hospital and outreach services at three centres of the Aravind Eye Care System (Coimbatore, Tirunelveli and Madurai, Aravind Eye Care System (AECS)) from 1 March 2002 to 29 February 2004.

Preceding and throughout recruitment, community awareness regarding signs of eye disease in children was created through posters placed at primary health centres and other strategic locations in the targeted districts. Parents were encouraged to bring children with eye signs suspicious of CRS to AECS for examination.

Additionally, a total of 2263 community outreach eye camps were conducted; with precamp publicity across 39 799 villages through large billboard-style poster displays, leaflets, and notices in local newspapers, radio, television and loud speaker announcements.

Physicians, healthcare workers and school teachers were given awareness about eye diseases of the paediatric age group during 4–8 h seminars and were requested to refer children with suspicious CRS findings, since AECS is the predominant paediatric eye care service provider in the target population.

Case definitions

A child between birth and 59 months of age with any of the following features; cataractous lens opacity in either or both eyes, corneal clouding or opacification, congenital glaucoma, iris hypoplasia, pigmentary retinopathy, globe anomalies such as microphthalmos or postencephalitis sequelae such as mental retardation, developmental delay, optic atrophy, nystagmus or pale discs was defined as being a CRS suspect case. This definition was accepted with or without a history of antenatal febrile rash in the mother.[5]

Clinical confirmation was based on fulfilment of WHO definition, which states that a clinically confirmed case is one in which any two of the following symptoms and signs from Group A, or one from each group is detected. Group A comprises congenital cataract(s) and/or congenital glaucoma, congenital heart disease, loss of hearing, pigmentary retinopathy; Group B comprises purpura, hepato-splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease and jaundice with onset within 24 hours after birth.

The clinical diagnosis was confirmed in all these cases by the principal investigator, and laboratory confirmation was based on a positive test for IgM antibodies in the blood sample.[10] The results on all cases were reviewed by an expert panel to classify cases.

Abbreviations: ACES, Aravind Eye Care System; CRS, congenital rubella syndrome

Ethical procedures

The study protocol was approved by the Institutional Review Board of AECS, the Indian Council of Medical Research (New Delhi) and the Secretariat Committee for Research on Human Subjects, WHO (Geneva).

Parents of children meeting the suspected CRS case definition were provided information about the study, and their child was enrolled upon obtaining informed parental consent.

Clinical examinations

All children had an ocular examination including tonometry using either the Pulsair 2000 (Keeler, Windsor, UK), or Tonopen XL (Mentor, Jacksonville, FL), slit lamp examination to study the structure of the iris and status of the pupil, and the fundus was examined using dilated direct and indirect ophthalmoscopy. Corneal diameter was measured using the Castroviejo Calliper when applicable.

A complete physical examination of all 1090 children was performed by a paediatrician with a detailed antenatal history from the mother, including receipt of rubella vaccination, of having undergone rubella diagnostic tests, a history of fever with (FMPR) or without maculo-papular rash during pregnancy, or of exposure in pregnancy to persons with FMPR. Children identified as having cardiac disease were examined by a specialist in that field.

Laboratory confirmation

One millilitre of venous blood was collected from CRS suspects, and tested for rubella-specific IgM and IgG antibodies at Aravind Eye Hospital laboratory, Madurai using four commercial IgM kits (Human, Wiesbaden, Germany; Behring Enzygnost, Marburg, Germany; Radim, Pomezia, Italy; Denka seikan, Tokyo, Japan) and the Behring Enzygnost IgG kit. Sera from infants aged 0–23 months were tested for antirubella IgM and IgG antibodies, and the remaining children were tested only for IgG. A positive result obtained with at least three out of four IgM kits was considered as laboratory-confirmed CRS. The Health Protection Agency, London, served as the reference laboratory for the study and ensured quality control.

A child was considered a laboratory-confirmed CRS by the expert panel if (1) their serum specimen was rubella IgM-positive for at least three recommended kits and rubella IgG-positive, and (2) if available, a follow-up serum specimen was also rubella IgG-positive. The diagnosis of CRS could not be excluded if (1) a child of 6 months or older at enrolment had only one positive rubella IgM test and was IgG-positive or (ii) a child of 12 months or older at enrolment had a negative rubella IgM test and was IgG-positive where the possibility of recent rubella infection could not be excluded.

Data analysis

Data were double-entered using EpiInfo software version 6.04 (Centres for Disease Control and Prevention, Atlanta, GA, and WHO, Geneva). Statistical analysis was performed using STATA software version 8.1 (STATA Corporation, College Station, TX).

RESULTS

Altogether 51,548 children in the age group of 0–59 months were screened. This included children attending the base hospital and all sites of outreach activities of AECS. Of the 1090 children suspected as having CRS, 622 were 0–11 months of age, and 468 were 12–59 months of age, with the mean age at presentation being 4.4 ± 3.2 months and 30.2 ± 13.8 months, respectively.

The findings from antenatal and perinatal history concluded that the child was the firstborn in 40% of cases; for 34.2%, there had been one preceding pregnancy, 16.8% of mothers had two pregnancies preceding the birth of the CRS suspect child, and the rest were grand-multipara.

Eight out of 1090 mothers had been vaccinated against rubella; 30.8% (336/1090) had a febrile episode during pregnancy. Fever with maculopapular rashes (FMPR) occurred in 24.7% (83/336), but only one person had a laboratory-confirmed episode of antenatal rubella infection. FMPR had occurred during the first trimester in 45.8% (38/83). Seventy mothers had at least one exposure to an individual who had FMPR during pregnancy; 36.4% were exposed during the first trimester.

Birth history was provided on 98.9% (1078/1090) of the CRS suspects; 91.4% (996) had been delivered at the end of a full-term pregnancy, and 77.9% of them were delivered *per vaginum*. Only 31.4% (298) of the children had a birth weight less than 2.5 kg. Abnormalities had been noticed at birth in 13.8% (150/1090) of infants, ranging from poor APGAR scores to the presence of multiple anomalies. At recruitment, congenital heart disease was found in 7.8% (85/1090) of children. Hearing (subjective clinical assessment) was normal in 81.2%; audiography could be reliably performed in less than 2% (13/992) of the children, and 21 children (45.7%) were small for gestational age.

Clinical examination (WHO definition) confirmed CRS in 299 (27.4%) of the suspects (table 2). Based on the serology of 1072 children, it was determined that CRS was present in 4.3% of the children and negative in 85%, and could not be excluded in the remainder (table 1).

Multivariable regression analysis revealed that a significant association continued to exist between clinical confirmation and the presence of cataract ($p<0.0001$), iris hypoplasia ($p<0.0001$) retinopathy ($p<0.0001$), micro cornea ($p = 0.003$) and glaucoma ($p<0.0001$), and between laboratory confirmation and the presence of cataract ($p<0.0001$), microcornea ($p<0.0001$) and glaucoma ($p = 0.002$) (table 2). The frequency and distribution of presenting eye signs are as summarised in table 2. We have disregarded the results for non-specific signs such as strabismus and nystagmus.

Clinically confirmed CRS occurred in 27.4% of suspected CRS, and laboratory-confirmed CRS in 4.3% of suspects. The

Table 1 Final classification of CRS cases decided by the expert panel

	In accordance with WHO definition (clinical signs)					
	0–11 months		12–59 months			
Expert panel decision	Yes	No	Yes	No	Total (%)	Inadequate serum
Positive	31 (2.9)	13 (1.2)	2 (0.2)		46 (4.3)	
Cannot exclude	1 (0.1)	1 (0.1)	53 (4.9)	57 (5.3)	112 (10.5)	
Negative	102 (9.5)	459 (42.8)	105 (9.8)	248 (23.1)	914 (85.2)	
Total	134 (12.5%)	473 (44.1%)	160 (14.9%)	305 (28.5%)	1072 (100.0)	18

Table 2 Distribution of CRS suspect eye signs in clinical and laboratory-confirmed patients

Eye signs	Suspects (n = 1090)	Clinically confirmed CRS (n = 299)	Odds ratio (95% CI)	MH χ^2 (p value)	Laboratory-confirmed CRS 46	Odds ratio (95% CI)	MH χ^2 (p value)
Microphthalmos	193	54	1.03 (0.73 to 1.46)	0.04 (0.85)	14	2.11 (1.10 to 4.05)	5.33 (0.02)
Cataract	538	223	4.43 (3.24 to 6.06)	104.78 (<0.0001)	37	4.46 (2.11 to 9.39)	18.54 (<0.0001)
Pupil rigidity	159	61	1.81 (1.27 to 2.58)	11.17 (0.0008)	10	1.67 (0.81 to 3.44)	1.97 (0.16)
Cloudy cornea	151	28	0.56 (0.36 to 0.87)	6.95 (0.008)	9	1.55 (0.73 to 3.27)	1.31 (0.25)
Corneal opacity	160	32	0.62 (0.41 to 0.94)	5.20 (0.02)	3	0.39 (0.12 to 1.29)	2.55 (0.11)
Microcornea	263	91	1.57 (1.16 to 2.13)	8.94 (0.003)	24	3.67 (2.01 to 6.71)	20.62 (<0.0001)
Iris hypoplasia	148	65	2.37 (1.65 to 3.40)	23.36 (<0.0001)	11	2.08 (1.03 to 4.20)	4.37 (0.04)
Glaucoma	92	31	1.38 (0.88 to 2.18)	1.98 (0.16)	7	2.03 (0.88 to 4.67)	2.85 (0.09)
Retinopathy	63	49	10.88 (5.76 to 20.56)	85.06 (<0.0001)	6	2.60 (1.05 to 6.39)	4.65 (0.03)
Optic Atrophy	49	11	0.76 (0.38 to 1.50)	0.64 (0.42)	1	0.46 (0.06 to 3.42)	0.60 (0.44)
Anophthalmos	22	2	0.26 (0.06 to 1.12)	3.79 (0.05)	0		

sensitivity, specificity and negative predictive values of these eye signs for detecting children with CRS were calculated (table 3).

DISCUSSION

The importance of CRS lies in the fact that it is a preventable multisystem disorder and that treating and rehabilitating these children is very demanding. Ocular abnormalities were found to occur in only 43% of children with CRS.[11] Since these signs are more evident at birth, this study was designed to screen for CRS, based on ocular signs in children.

It is interesting to note that, in this study, 28.2% (13/46) of children who were confirmed to have CRS and another 52% of (58/112) children where CRS could not be excluded based on the available serological results, did not meet the criteria of WHO definition (table 1). This confirms the fact that although the WHO definition is very useful for confirming CRS cases, broadening the definition by including the full spectrum of eye signs associated with CRS may be useful to improve the sensitivity for screening.

Among those with eye signs, the presence of cataract (37/46) seems to hold the strongest association with CRS, of which 11 children had only cataract with no other systemic manifestations at presentation. Interestingly, none of the signs used for screening showed a high sensitivity when used individually, emphasising that a panel of signs should be elicited for suspecting CRS. The high specificity of signs like retinopathy, iris hypoplasia and pupillary rigidity leads to the suggestion that the presence of these signs in a child with cataract is highly specific of CRS. Though the definitive diagnosis of rubella can only be made by specific laboratory methods, it is necessary to provide simple, broad and inclusive criteria that can be used by the medical community to identify suspicious cases of rubella.

Diagnosis of CRS is based on the detection of rubella-specific IgM and IgG after maternal antibody has declined. Rubella-specific IgM is generally lost in CRS cases by 6 months of age, and its estimation can be complicated by the quality of test used.[12] This holds good for this study which confirms that the majority of children who were positive for IgM fall under the age group of less than 6 months (table 3).

The group in which CRS could not be excluded was of a relatively older age and had suffered its disabling sequelae longer. They are the part of a larger pool of children who might have been confirmed to have CRS provided they were identified in early infancy or by employing more sophisticated laboratory methods, which is beyond the scope of this study. In 18 children where serum was difficult to obtain, they were either too small or too sick at presentation and were lost for follow-up suggesting that at least a few among them could be potential cases of positive CRS.

To our knowledge, there is no correct format existing in the country to document CRS, and so exact assessment of the burden of CRS is difficult. This is the first ever study conducted by an ophthalmologist to determine the prevalence of eye signs related to CRS and thereby helping indirectly to assess the disease burden in India. It is evident that screening for eye signs in infants is easier than for other systemic abnormalities like hearing, cardiac and central-nervous-system abnormalities, since these signs are detectable only in later life. The experience of the study also indicates that ophthalmologist can identify a considerable number of suspected CRS cases based on eye signs tested in the study which has proved practical for CRS screening in children and can be recommended for other ophthalmologists.

There are several limitations of this study. First, children only with eye signs were screened for CRS. Second, children with CRS who were severely ill may have remained at home without medical attention or died. Third, children with hearing problems (the commonest finding occurring due to maternal infection at second trimester) were not included in this study.

Table 3 Significance of eye signs in detecting CRS (both clinically and laboratory)

		Clinically confirmed (%)			Laboratory-confirmed (%)		
Eye signs	Total no. of suspects	Sensitivity	Specificity	NPV	Sensitivity	Specificity	NPV
Cataract	538	74.6	60.2	86.2	80.4	52.0	98.4
Pupil rigidity	159	20.4	87.6	74.4	21.7	85.7	96.1
Cloudy cornea	151	9.4	84.5	71.1	19.6	86.4	96.1
Corneal opacity	160	10.7	83.8	71.3	6.5	85.0	95.4
Microcornea	263	30.4	78.3	74.9	52.2	77.1	97.3
Iris hypoplasia	148	21.7	89.5	75.2	23.9	86.9	96.3
Retinopathy	63	16.4	98.2	75.7	13.0	94.5	96.1

NPV, negative predictive value.

Finally, although AECS has a widespread community outreach, it is not the only healthcare resource in the study areas and hence it is possible for a considerable number of children to attend other facilities.

Although CRS has been eliminated in many developed countries, it is still a menace in a developing country like India. This study confirms the presence of CRS in the country (southern region) and its magnitude, and we sincerely hope that strategies will be developed to study the prevalence of this disease in other parts of the country, leading to policy debate aimed towards its prevention by immunisation.

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