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


EXTENDED REPORT


See end of article for authors’ affiliations

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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 fulfillment 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.

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.
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 Tonometer 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; Radium, Pomezia, Italy; Denka seiken, 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), microcornea (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
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 be associated with a considerable number of suspected CRS cases based on eye signs. The presence of these signs in a child with cataract is highly suggestive that at least a few among them could be potential cases of positive CRS.

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

<table>
<thead>
<tr>
<th>Eye signs</th>
<th>Suspects (n = 1090)</th>
<th>Clinically confirmed CRS (n = 299)</th>
<th>Odds ratio (95% Cl)</th>
<th>MH χ² (p value)</th>
<th>Laboratory-confirmed CRS 46</th>
<th>Odds ratio (95% Cl)</th>
<th>MH χ² (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microphthalmos</td>
<td>193 54</td>
<td>1.03 (0.73 to 1.46)</td>
<td>0.04 (0.85)</td>
<td>14</td>
<td>2.11 (1.10 to 4.05)</td>
<td>5.33 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>538 223</td>
<td>4.43 (3.24 to 6.06)</td>
<td>104.78 (&lt;0.0001)</td>
<td>37</td>
<td>4.46 (2.11 to 9.39)</td>
<td>18.54 (&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Pupil rigidity</td>
<td>159 61</td>
<td>1.81 (1.27 to 2.58)</td>
<td>11.17 (0.0008)</td>
<td>10</td>
<td>1.67 (0.81 to 3.44)</td>
<td>1.97 (0.16)</td>
<td></td>
</tr>
<tr>
<td>Cloudy cornea</td>
<td>151 28</td>
<td>0.56 (0.36 to 0.87)</td>
<td>6.95 (0.008)</td>
<td>9</td>
<td>1.55 (0.73 to 3.27)</td>
<td>1.31 (0.25)</td>
<td></td>
</tr>
<tr>
<td>Corneal opacity</td>
<td>160 32</td>
<td>0.62 (0.41 to 0.94)</td>
<td>5.20 (0.02)</td>
<td>3</td>
<td>0.39 (0.12 to 1.29)</td>
<td>2.55 (0.11)</td>
<td></td>
</tr>
<tr>
<td>Microcornea</td>
<td>263 91</td>
<td>1.57 (1.16 to 2.13)</td>
<td>8.94 (0.003)</td>
<td>24</td>
<td>3.67 (2.01 to 6.71)</td>
<td>20.62 (&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Iris hypoplasia</td>
<td>148 65</td>
<td>2.57 (1.65 to 3.40)</td>
<td>23.36 (&lt;0.0001)</td>
<td>11</td>
<td>2.06 (1.03 to 4.20)</td>
<td>4.37 (0.04)</td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td>92 31</td>
<td>1.38 (0.88 to 2.18)</td>
<td>1.98 (0.16)</td>
<td>7</td>
<td>2.03 (0.88 to 4.67)</td>
<td>2.85 (0.09)</td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>63 49</td>
<td>10.88 (5.76 to 20.56)</td>
<td>85.06 (&lt;0.0001)</td>
<td>6</td>
<td>2.60 (1.05 to 6.39)</td>
<td>4.65 (0.03)</td>
<td></td>
</tr>
<tr>
<td>Optic Atrophy</td>
<td>49 11</td>
<td>0.76 (0.38 to 1.50)</td>
<td>0.64 (0.42)</td>
<td>1</td>
<td>0.46 (0.06 to 3.42)</td>
<td>0.60 (0.44)</td>
<td></td>
</tr>
<tr>
<td>Anophthalmos</td>
<td>22 2</td>
<td>0.26 (0.06 to 1.12)</td>
<td>3.79 (0.05)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Eye signs</th>
<th>Total no. of suspects</th>
<th>Clinically confirmed (%)</th>
<th>Laboratory-confirmed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Cataract</td>
<td>538</td>
<td>74.6</td>
<td>60.2</td>
</tr>
<tr>
<td>Pupil rigidity</td>
<td>159</td>
<td>20.4</td>
<td>87.6</td>
</tr>
<tr>
<td>Cloudy cornea</td>
<td>151</td>
<td>9.4</td>
<td>84.5</td>
</tr>
<tr>
<td>Corneal opacity</td>
<td>160</td>
<td>10.7</td>
<td>83.8</td>
</tr>
<tr>
<td>Microcornea</td>
<td>263</td>
<td>30.4</td>
<td>78.3</td>
</tr>
<tr>
<td>Iris hypoplasia</td>
<td>148</td>
<td>21.7</td>
<td>89.5</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>63</td>
<td>16.4</td>
<td>98.2</td>
</tr>
</tbody>
</table>

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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Competing interests: None declared.

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