Potential causes of congenital infection include viruses - cytomegalovirus (CMV), rubella virus (RV), herpes simplex virus (HSV), entero virus, hepatitis C virus, human immunodeficiency virus (HIV), human herpesvirus (types 6, 7 & 8), lymphocytic chorio meningitis virus, parvo virus, varicella zoster virus and parasite Toxoplasma gondii (T. gondii)\(^1\). TORCHES infections (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex virus and Syphilis by Treponema pallidum) in the mother are some of the most common infections that can lead to foetal anomalies or even foetal loss\(^2\). Common ocular manifestations of congenital infections include chorioretinitis and cataract, with less common occurrence of microphthalmos, glaucoma, keratitis, microphthalmia, iridocyclitis, iris dystrophy, optic neuritis, retinitis\(^3\).
Prevention of visual impairment due to congenital and infantile cataract is an important component of the World Health Organization International Program for the Elimination of Avoidable Blindness by 2020. Congenital cataract affects about 3/10,000 newborns in India and is the most serious type of childhood cataract because of its potential for inhibiting or restricting early visual development and in India, 7.4-15.3 per cent of childhood blindness is due to cataract. Congenital cataract is responsible for more than one million childhood blindness in Asia with about 50,000 being added every year in India. The various causes of congenital cataract can be prenatal infections due to RV, T. gondii, CMV, HSV and T. pallidum, prenatal drug exposure, prenatally exposed fetuses and children, peri-natal metabolic disorders, hereditary, or unknown aetiology. IgM antibodies are produced in the foetus in response to any infection and are specific for foetal infection, as IgM cannot cross the placental barrier. A few studies carried out in India to know the infectious aetiology of congenital cataract have been predominantly on rubella virus and a couple on herpes simplex virus and one on T. gondii. The various criteria used for classifying an infectious agent to be associated with congenital cataract include demonstration of the specific IgM antibodies in the serum, isolation of the infectious agent and detection of the nucleic acid of the infectious agent from various clinical specimens from the infected foetus or newborn. However, there are no comprehensive reports on the association of TORCHES with congenital cataract. The present hospital-based study was performed to know the infectious aetiology of congenital cataract based on the presence of IgM antibodies to TORCHES in the serum of congenital cataract patients attending a tertiary care eye hospital in Chennai, south India.

**Material & Methods**

**Patients:** A total of 593 infants and children clinically diagnosed as congenital cataract (with or without other congenital manifestations) at Sankara Nethralaya, a referral eye hospital in Chennai, during the period January 1998 - December 2006 were included in the present study. Peripheral blood (1-2 ml) was collected by venipuncture or femoral tap by qualified plebotomists with prior consent of the parents or guardians of the children. These were 368 (62.1%) males and 225 (37.9%) females in the age group of 10 days to 12 months. Blood samples collected from all children were tested for the presence of specific IgG and IgM antibodies to T. gondii, RV, CMV, HSV by ELISA and specific anti-treponemal antibodies by T. pallidum haemagglutination test (TPHA).

**Methods:** Assay of specific anti T. gondii IgG, anti T. gondii IgM, anti rubella IgG, anti rubella IgM, anti CMV IgG, anti CMV IgM, anti HSV-1 IgG, anti HSV-2 IgG, and anti HSV IgM antibodies were performed respectively by ELISA using commercially available ‘bioelisa’ kits, (Biokit, SA, Spain) following manufacturer’s instructions. The test for the detection of specific IgM antibodies to T. gondii/ RV/ CMV /HSV was performed by the immuno-capture technique to rule out non specific detection of IgM antibodies. To describe the procedure in brief, the immuno-capture ELISA was performed by incubating the diluted test sera in microwell plates coated with rabbit antibodies to human IgM. Subsequently, the wells were washed to remove residual test sera, and the specific antigen (T. gondii/ RV/ CMV /HSV) conjugated with enzyme was added. The sera for IgG and IgM antibodies were tested at dilution of 1:100, along with the positive and negative controls in each run. The final readings were taken in ELISA reader (Bio-Tek Instruments Inc., USA, and Model EL 311) at 450 nm with reference at 620 nm. Presence of antibodies at dilution of >1:100 were considered positive. Anti- T. pallidum antibodies were tested by TPHA test (Immutrep TPHA, Omega Diagnostics Ltd., Scotland, UK) following manufacturer’s instructions.

**Statistical analysis:** Data were analysed by Friedman test- Chi square test and P<0.05 was considered significant.

**Results**

Majority of patients (74, 12.5%) were in the age group of 5-6 months, followed by 68 (11.5%) in 2-3 months and the least (21, 3.5%) in 10-11 months (Fig. 1).

**Fig. 1.** Age- and sex-wise distribution of the congenital cataract patients (n = 593).
IgM class of antibodies alone was detected against *T. gondii* in 7, RV in 14, CMV in 8, and HSV in 13, both IgG and IgM antibodies in 3, 36, 38 and 17, and IgG alone in 50, 112, 354 and 59 respectively (Table I). All the 593 serum samples were negative for the presence of anti-treponemal antibodies by TPHA. The presence of IgM antibodies was highest against RV (8.4%) followed by CMV (7.8%), HSV (5.1%) and *T. gondii* (1.7%). Presence of IgM antibodies to *T. gondii* in the study group was significantly lower (*P*=0.001) when compared to IgM antibodies to RV, CMV and HSV. The presence of IgG antibodies was highest against CMV (66.1%), followed by RV (25%), HSV (10.2%) and *T. gondii* (8.9%). Antibodies to *Treponema pallidum* was not detected.

Age- and sex-wise distribution of the IgM antibodies to *T. gondii*, RV, CMV and HSV by ELISA in the 593 patients is shown in Fig. 2. The IgM antibodies were highest in the age group of 8-9 months in the males and < 1 month in the females. The age-wise distribution of IgM antibodies to *T. gondii*, RV, CMV and HSV is given in Fig. 3. IgM antibodies to *T. gondii* was highest (6.7%) in the age group of 8-9 months, RV (22.6%) in the age group of less than 1 month, CMV (13.3%) in 8-9 months and HSV (9.5%) in 10-11 months respectively. IgM antibodies to one of the four infectious agents detected in 72 (19.6%) males and 48 (21.3%) females were statistically not significant (Table II). The presence of IgM antibodies among the males and females against *T. gondii*, RV, CMV and HSV respectively were not significantly different. IgM antibodies to one or more of the four infectious agents were highest in the age group below one month (28.3%) and lowest in the age group of > 9 - < 10 months (7.4%). The presence of IgM antibodies to one or more of the four infectious agents was significantly more in the age group of <1, >2-<3, >7-<8 months compared to the other age groups (*P*<0.001).

### Table I. Distribution of the presence of antibodies to TORCHES in 593 congenital cataract patients

<table>
<thead>
<tr>
<th>Organism to which antibodies were tested</th>
<th>Number of congenital cataract patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab to <em>T. gondii</em></td>
<td>IgM alone detected</td>
</tr>
<tr>
<td>Ab to RV</td>
<td>7</td>
</tr>
<tr>
<td>Ab to CMV</td>
<td>14</td>
</tr>
<tr>
<td>Ab to HSV-1 and HSV-2</td>
<td>8</td>
</tr>
<tr>
<td>Number of patients with specific antibodies to one infectious agent</td>
<td>32</td>
</tr>
<tr>
<td>Number of patients with antibodies to two or more infectious agents</td>
<td>5</td>
</tr>
<tr>
<td>Total no of patients with antibodies to TORCHES*</td>
<td>37</td>
</tr>
</tbody>
</table>

Ab, antibodies; *one patient had IgM antibodies to *T. gondii* and both IgG and IgM antibodies to Rubella virus; Antibodies to *Treponema pallidum* was not detected in any of the 593 patients. **IgG antibodies to HSV-1 was detected in 15 patients and HSV-2 in 2 patients.

Values in parentheses are percentages.
Overall, IgM antibodies to atleast one of the four infectious agents (T. gondii, RV, CMV, HSV) were detected in 120 (20.2%) patients. IgM antibodies were detected against T. gondii alone in 5, RV alone in 39, CMV alone 40 and HSV alone 21 with a total of 105 (17.7%) patients. IgM antibodies against two or more infectious agents were detected in 15 (2.5%) patients which included specific IgM antibodies to both HSV and RV in 6, T. gondii and CMV in 2, T. gondii and RV in 2, CMV and HSV in 1, T. gondii and HSV in 1, and against CMV, HSV and RV in one patient.

**Discussion**

Prenatal diagnosis of congenital infections is based on ultrasonography, amniocentesis and foetal blood sampling. The detection of IgM or IgA antibodies to infectious agents in an infant is highly sensitive for the diagnosis of congenital infections. The major causes of visual impairment and blindness in 1318 children attending the school for the blind in India were vitamin A deficiency, congenital ocular anomalies, inherited retinal dystrophies and cataract. In a study by Angra, the causes of non-traumatic cataract in 366 children were hereditary (25%), congenital rubella syndrome (CRS) (15%) and undetermined (51%). In another study by Johar et al., on paediatric non-traumatic cataract in western India, 7.2 per cent were hereditary, 4.6 per cent due to CRS, 15 per secondary cataract and 73 per cent were undetermined.

Normally, the diagnosis of congenital infections is based on serological demonstration of IgM, but specific IgM antibodies are frequently not present as antibody synthesis is often delayed and may not begin until some months after birth in 25 per cent of cases. The percentage of infants who are IgM positive declines over the first year of life, until at one year, most infants are IgM negative. The absence of the antibodies to the aetiological agents in congenital cataract patients may be due to the fact that, the primary infection of the lens would have been in the central lens fibers at a stage when immunological apparatus had not attained maturity to react to the viral antigen and the developing immune system has considered it as self-antigen.

These are only a few sporadic case reports from India on congenital toxoplasmosis and there are no published reports on seroprevalence in congenital cataract patients. However, we reported detection of T. gondii DNA in 32.7 per cent of lens aspirate from congenital cataract patients.

Congenital rubella syndrome is an important cause of deafness, heart disease, cataract, mental retardation and variety of other permanent sequelae in children. The seroprevalence of CRS among congenital malformed babies was 12 per cent in 1991 and varied from 0.6-34.5 per cent during the period 1998-2002. In a study of 485 congenital cataract patients by Angra & Moghan, the prevalence of rubella cataract, based on serology and isolation of the virus, was 11.3 per cent. Earlier published reports from India, detected IgM antibodies to RV in 4.6-24.5 per cent of congenital cataract patients compared to 8.4 per cent in the present study. The ocular manifestations of CRS can be detected much earlier than heart abnormalities, hearing impairment and mental retardation in the newborns, so early diagnosis leads to early treatment and better management of the infected child.
Anti CMV IgM antibodies were detected in 18.8-20 per cent of newborns with various congenital anomalies in Delhi, and there are no reports on seroprevalence of CMV infection in congenital cataract patients from India. Neonatal herpes usually results from infection of the newborn by virus secreted into the mothers' genital tract during labour and delivery, compared to rare cases of intrauterine infections, and ocular manifestations are conjunctivitis, keratitis, microphthalmia, cataract, iridocyclitis, iris dystrophy, optic neuritis, retinitis, and chorioretinitis. Both HSV types 1 and 2 have been associated with neonatal ocular infections, whereas 80 per cent of neonatal herpes is caused by HSV type-2. Anti HSV-1 IgM antibodies and the HSV -1 DNA was detected in 4 cases of congenital cataract patients in Hyderabad. In the present study, one ELISA kit which could detect IgM antibodies to both HSV-1 and HSV -2 was used, so the actual prevalence of HSV-1 or HSV-2 infection could not be done. However, among these 30 patients with IgM antibodies to HSV, anti HSV-1 IgG was also detected in 15 patients and anti HSV-2 IgG in 2.

IgG antibodies in the newborns may be of maternal origin and can persist for up to 6 months. In this study, as the antibodies to TORCHES were not analysed in the mothers' serum, the clinical significance of the presence of IgG antibodies to T. gondii/ RV/CMV/HSV in the infants could not be analysed.

Co-infections with more than one infectious agent was detected in 17.7 per cent of the congenital cataract patients in this study compared to 33.3 per cent by Thapliyal et al and 42.5 per cent by Turbadkar et al among newborns with congenital malformations. The kits used for the detection of specific IgM antibodies in this study, are based on the principle of immunocapture and hence the non specificity of the IgM antibody detection system was ruled out as the reason for co-infection.

The predominance of males in this study population may not indicate the actual increased prevalence of congenital cataract among males, but may be because of the fact that any illness in the male child is given more importance in India. None of the patients included in this study were positive for antibodies to HIV (data not included).

In conclusion, the present study showed that 20.2 per cent of congenital cataract patient had IgM antibodies and 12 per cent of these harboured IgM antibodies to more than one infectious agent (except T. pallidum), indicating the association of TORCHES agents in congenital cataract.

References


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