

Is 20/20 visual outcome a reality in rubella cataract? - Prognostic factors in children with cataract associated with congenital rubella syndrome

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Purpose: The aim of this study was to evaluate prognostic factors associated with final visual outcome in patients with congenital cataract associated with congenital rubella syndrome. **Methods:** A prospective interventional analysis of preoperative systemic and ocular features of 56 eyes of 28 seropositive infants of less than 12 months presenting to us with bilateral cataract was performed. All infants were surgically treated with cataract extraction, posterior capsulorhexis, and anterior vitrectomy followed by visual rehabilitation. Intraocular lens implantation was done in children after 2 years of age. Outcome data were collected till children reached the fifth chronological age. Chi-square test was used as a test of significance for qualitative data. **Results:** Of the 56 eyes, 44.6% eyes had vision better than 20/60. Important preoperative factors related to poor visual prognosis were morphology of cataract ($P = 0.004$), microphthalmos ($P < 0.001$), features suggestive of iris hypoplasia ($P < 0.001$), optic atrophy ($P < 0.001$), nystagmus ($P = 0.02$), and associated neurological anomalies ($P = 0.0023$). We found no significant statistical association between postoperative visual outcome and isolated rubella retinopathy, cloudy cornea, cardiological, and ontological abnormalities. **Conclusion:** Cataract associated with rubella is a common cause of congenital cataract in developing countries. Determining prognostic factors helps us in parent counseling and planning treatment protocols. Nevertheless, early detection and treatment with adequate multidisciplinary approach remains priority for improving long-term visual outcomes.

Key words: Congenital rubella syndrome, prognostic factors, Rubella cataracts, visual outcomes

Congenital rubella syndrome (CRS) resulting from maternal rubella infection in the first trimester affects an estimated 1,00,000 infants each year worldwide.^[1,2] Estimates suggest that 10%–30% of adolescent females and 12%–30% of women in the reproductive age-group are susceptible to rubella infection in India.^[3,4] It forms an undiagnosed epidemic in developing countries such as India due to poor immunization coverage.

Ocular manifestations form a major part of CRS, of which unilateral or bilateral cataract forms a hallmark.^[1] Rubella cataract can either be isolated or can be associated with varying degrees of either systemic or ocular anomalies which can affect visual outcomes postcataract surgery.^[5-8] Earlier works^[1,5] have aimed at studying the ocular and systemic manifestations and associated clinical spectrum in children with rubella cataracts, but factors prognostic for long-term visual outcomes have not been investigated.

The aim of this study was to assess visual outcomes and to determine preoperative ocular and systemic features that contribute to visual prognosis postcataract surgery. By doing so, we may provide additional information to treating surgeon, which helps in better counseling of parents and planning adequate management.

Methods

This was a prospective interventional study of systemic and ocular features of 56 eyes of 28 seropositive infants (<12 months) who presented with bilateral cataract to the

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Pediatric Ophthalmology department of a tertiary eye care center in South India. This study was approved by the ethical committee and the study was carried out in accordance with the approved guidelines. Informed consent was obtained from all parents before surgery.

Children with unilateral cataract and who were noncompliant for follow-up, wear of aphakic glasses, or amblyopia treatment regimen were excluded from the study.

History of maternal fever with rash in early month of gestation was taken from all parents and was positive in 16 mothers. Seropositivity in infants was confirmed by showing IgM and nonrapidly declining IgG antibodies using the human ELISA kit. Preoperatively all infants underwent detailed anterior and posterior segment evaluation. Thorough systemic evaluation including MRI, echocardiography, and BERA was performed by a pediatrician.

All infants were surgically treated with cataract extraction, posterior capsulorhexis, and anterior vitrectomy. Secondary intraocular lens implantation was done between 24 and 48 months of child's chronological age. In eyes with microphthalmos and microcornea, a customized intraocular lens was implanted [Fig. 1]. All surgeries were performed by the same team of surgeons.

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Children were followed up at weekly intervals till 6 weeks, monthly till 6 months, 3 monthly till 2 years, and 6 monthly thereafter. During each visit visual acuity (VA) assessment by Tellers chart, Lea symbol chart or Snellen’s chart depending on the age of the child, slit-lamp examination, intraocular pressure (IOP), and fundus examination were carried out. Children were given refractive correction. Those children who had no full visual improvement with full refractive correction were advised occlusion therapy. VA at the end of 5 years of child’s chronological age, assessed using Snellen’s chart was considered for statistical analysis.

Parameters collected were then correlated using statistical parametric and nonparametric methods. Continuous data were represented as mean and standard deviation. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as a test of significance for qualitative data. A value of $P < 0.05$ (probability that the result is true) was considered as statistically significant after assuming all the rules of statistical tests.

Results

1. Study population

In the study 42.9% were males and 57.1% were females. 17.9% were aged <3 months, 42.9% were in the age group 4–6 months, 32.1% were in the age group 7–9 months and 7.1% were in the age group >9 months. Based on VA at the end of 5 years, children were divided into three groups:

- 20/60 or better: Group 1–25 eyes (44.64%)
- 20/80-20/200: Group 2–19 eyes (33.92%)
- less than 20/200: Group 3–12 eyes (21.42%)

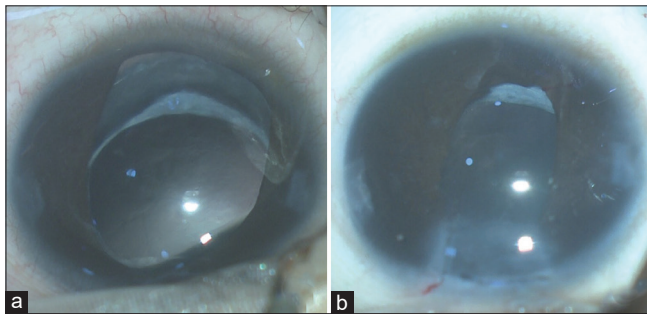


Figure 1: (a) Microphthalmic eye post primary cataract extraction with aphakia; (b) same eye after secondary customized intraocular lens placement

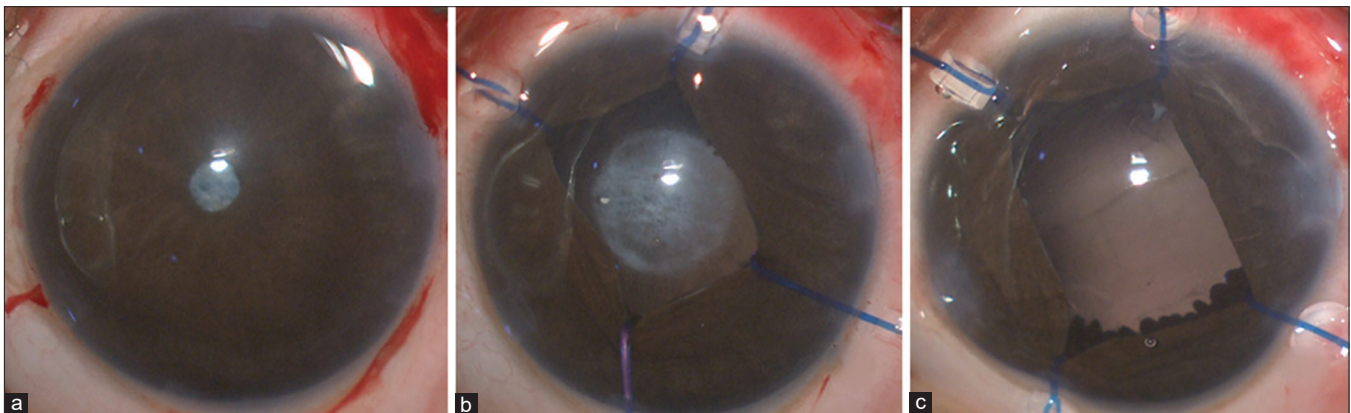


Figure 2: (a) Eye with non-dilating pupil and membranous cataract (b) iris hooks inserted to aid cataract surgery (c) Postoperative image of the same eye with primary aphakia

The median age of surgery for these infants were 5 months (mean, 6.2; range, 2 to 10).

2. Ocular manifestations and visual outcomes

The most common morphology of rubella cataract noted was total cataract (41.07%) and this was followed by zonular cataract (32.14%), membranous cataract (16.07%), and others (10.71%) in that corresponding order. Overall, there was not much variation in number of eyes having VA better than 20/60 in any of the groups but the number of eyes with VA less than 20/200 was significantly more in membranous cataract group (44.4%) as compared to other groups, $P = 0.004$, [Table 1]

Twenty-two eyes had microphthalmos, of which 20 eyes had microcornea. In 22 eyes (39.28%) with microphthalmos, three eyes (13.6%) had VA better than 20/60, nine eyes (40.9%) had VA better than 20/200 and 10 eyes (45.5%) had VA less than 20/200. There was a significant difference in VA with respect to the presence and absence of microphthalmos, $P < 0.00$, [Table 2]

Twenty (35.71%) eyes in our series had features of iris hypoplasia suggested by pin point or nondilating pupils [Fig. 2], posterior synechiae, or coloboma. Iris hypoplasia did adversely affect visual outcome with 50% eyes having VA less than 20/60, $P < 0.001$, [Table 3]

Preoperatively, corneal involvement in the form of fine corneal stippling and corneal edema in the absence of elevated IOP was noted in 18 eyes (32.14%) and two eyes (3.57%), respectively. Presence of either of these did not have any negative effect on final visual outcomes with nearly 38.9% of eyes with fine mottling and 100% of eyes with corneal edema having final VA better than 20/60, $P = 0.598$. Corneal edema was noted to resolve spontaneously over 4–6 months

Among eyes with isolated rubella retinopathy, 13 eyes (43.3%) had VA better than 20/60, nine eyes (30%) had VA of 20/60-20/200 and eight eyes (26.7%) had VA of less than 20/200; no significant association between Chorioretinitis and Final Visual Acuity, ($P = 0.56$). Six eyes (10.71%) had optic atrophy (partial/total) in addition to rubella retinopathy, optic nerve involvement did have a negative effect on final visual outcome, ($P < 0.001$)

In eyes with nystagmus, five eyes (8.92%) had VA better than 20/60, 13 eyes (59.1%) had VA of 20/60 to 20/200 and four eyes (18.2%) had VA of less than 20/200, obviously highlighting the fact that presence of nystagmus adversely affects visual prognosis in eyes with rubella cataracts, $P = 0.02$, [Table 4]

Table 1: Correlation between morphology of cataract and visual outcomes

	Final Visual Acuity						<i>P</i>
	Group 1		Group 2		Group 3		
	Count	%	Count	%	Count	%	
Type of Cataract							
Zonular	10	55.6%	6	33.3%	2	11.1%	0.004*
Total	10	43.5%	7	30.4%	6	26.1%	
Membranous And Absorbed	5	55.6%	0	0.0%	4	44.4%	
Others	0	0.0%	6	100.0%	0	0.0%	

Table 2: Correlation between microphthalmos and visual outcomes

	Final Visual Acuity						<i>P</i>
	Group 1		Group 2		Group 3		
	Count	%	Count	%	Count	%	
Microphthalmos							
No	22	64.7%	10	29.4%	2	5.9%	<0.001*
Yes	3	13.6%	9	40.9%	10	45.5%	

Table 3: Association between Iris hypoplasia and visual acuity

	Final Visual Acuity						<i>P</i>
	Group 1		Group 2		Group 3		
	Count	%	Count	%	Count	%	
Iris Hypoplasia							
No	24	66.7%	10	27.8%	2	5.6%	<0.001*
Yes	1	5.0%	9	45.0%	10	50.0%	

Table 4: Nystagmus vs Visual outcomes

	Final Visual Acuity						<i>P</i>
	Group 1		Group 2		Group 3		
	Count	%	Count	%	Count	%	
Nystagmus							
No	20	58.82%	10	29.41%	4	11.76%	0.02*
Yes	5	8.92%	13	59.1%	4	18.2%	

Table 5: Association between neurological abnormality and visual outcomes

Neurological Abnormality	Final Visual Acuity						<i>P</i>
	20/20 to 20/40		20/50 to 20/125		>20/200		
	Count	%	Count	%	Count	%	
Normal	25	62.5%	15	37.5%	0	0.0%	<0.001*
Isolated Microcephaly	0	0.0%	2	100.0%	0	0.0%	
Isolated Psychomotor Retardation	0	0.0%	0	0.0%	4	100.0%	
Multiple Neurological Deficits + Seizures	0	0.0%	0	0.0%	8	100.0%	
Hydrocephalus	0	0.0%	2	100.0%	0	0.0%	

Two eyes had glaucoma preoperatively, both associated with microphthalmic eyes and were surgically treated with

trabeculectomy, four children were noted to have strabismus which was managed conservatively by patching. There was

no significant association between preoperative glaucoma/strabismus and final VA if they were managed adequately at appropriate time.

3. Systemic findings and final visual outcomes

Associated cardiological and otological anomalies were noted in eight and eleven infants, respectively. There was no significant association between cardiological abnormality, ($P=0.347$) or otological abnormality, ($P=0.795$) with final visual recovery

Neurological abnormalities when present significantly affected visual outcome negatively ($P = 0.0023$). In eyes of children with Isolated Microcephaly 100% had VA of 20/60 to 20/200 and in among those with Isolated Psychomotor Retardation and seizures, 100% had VA of less than 20/200. In children with hydrocephalus, 100% had VA in the range of 20/60 to 20/200 [Table 5].

Discussion

Birth defects with CRS is reported to be 90% when infection occurs within the first 10 weeks of pregnancy.^[9,10] CRS affects almost all ocular structures, either in isolation or in combination with systemic anomalies. Multiple studies^[1,5,6,8] have reported various ocular and systemic manifestations and variations in wide clinical spectra of CRS. However, to the best of our knowledge no study has specifically addressed the preoperative ocular and systemic factors prognostic for long-term visual outcomes in children associated with rubella cataracts. Such information is important for the planning of child's surgery, follow-up and counseling of parents.

In CRS, the fetus synthesizes its own immunoglobulin (IgM antibodies) persisting for 18 months postnatally. Sensitivity of IgM estimation for the diagnosis of CRS reduces from 100% before 5 months, 60% up to 12 months, and 40% by 18 months.^[11] In our study as children were below 12 months of age, selection of cases was based on seropositivity of these antibodies by human ELISA kit.

The virus enters the lens before the development of the lens capsule that would otherwise act as barrier to the virus.^[4,12-15] Though nuclear cataract is the most common morphology, postnatally the lens acts as a reservoir for the virus, which converts nuclear into total cataract. In our study total cataract was the most common due to maximum patients being above the age of 4 months. The visual outcomes were better in eyes with zonular cataract as compared to membranous and total cataract which is consistent with previous studies by Vijayalakshmi *et al.*^[5] This could be attributed to the fact that eyes with zonular cataract had a peripheral relatively lucid area which did continue to act as a source of visual stimulation.

Association of rubella cataract with microphthalmos and iris hypoplasia is as high as 60% to 90%.^[1,15-17] Presumably the virus-induced delay in maturation and replication of the affected cells is responsible for microphthalmos and microcornea, and it on a larger scale can be termed as "failure to thrive."^[18] Similarly, impairment in maturation of dilator pupillae and necrosis of iris pigment epithelium can result in iris abnormalities like iris hypoplasia and rigid pupils. In our study, both microphthalmos and iris abnormalities together and individually adversely affected visual outcomes with only 13.6% eyes with microphthalmos and 50% of eyes with iris abnormalities having satisfactory visual outcomes. Iris hypoplasia and microphthalmos, with time, go on to cause further ocular problems in patients, the most common being

glaucoma. Moreover, the pathogenesis of CRS being incomplete development, this may not be restricted to iris or eye per se. The process of maldevelopment may have an extension in the intricate visual pathway or neural networks, which needs to be further evaluated and beyond the scope of these articles and which may justify the reduced visual outcomes in eyes with microphthalmos and iris abnormalities.

Inapparent viral infiltration of developing corneal endothelium is implicated in absent Descemet's membrane, deep interstitial keratitis, stromal corneal swelling, and deranged, focally absent endothelial cells.^[18] In our study involvement of cornea as corneal edema or fine mottling in the absence of elevated IOP was found in 35.71% eyes which did not interfere with either surgery or postoperative visual recovery. A few authors believe that corneal edema in CRS could be more a consequence of secondary glaucoma,^[18,19] but point to be noted is the two eyes in our study with preexisting glaucoma which had corneal edema tended to have persistent generalized corneal edema till the IOP was adequately controlled, whereas the eyes with corneal edema in the absence of congenital glaucoma were usually focal or central with self-remission.

The retinopathy in CRS is variably reported from 13% to 61%.^[7,17,20,21] The pigment deposits may vary from fine powdery, sprinkled, or granular shapes throughout the retina to discrete patchy black lesions varying in size and location resembling retinitis pigmentosa.^[21] In our series, isolated rubella retinopathy was seen in 53.37% cases and six eyes (10.71%) eyes had coexisting optic atrophy of variable extent. Isolated rubella retinopathy being nonprogressive, final VA was unaffected by the pigmentary changes alone, but associated optic nerve or macular involvement can significantly affect final visual outcomes.

In our study, eyes with nystagmus were six times more likely to achieve vision worse than 20/60. This finding is congruent with previous studies by Yamamoto *et al.*^[22] and Lambert *et al.*^[23] These studies supplement our findings that nystagmus detrimentally affects the critical period of vision development, leading to poor visual outcomes long-term. For some patients, congenital nystagmus was present before the cataracts became visually significant, whereas others developed nystagmus as a result of early sensory deprivation.

Congenital glaucoma is an infrequent finding following maternal rubella, caused either by failure of absorption of the mesoderm of the angle or by failure of the canal of Schlemm to differentiate.^[24,25] In our study, two eyes with primary glaucoma was managed surgically for glaucoma followed by amblyopia management. Glaucoma and strabismus were not found to have any significant impact on final visual outcome if they were managed in right way at the right time. Though almost all systems can be affected in CRS, the defects of hearing, cardiovascular system, and central nervous system have been well documented. We did not find any correlation between cardiological and otological abnormalities with final VA. Developmental and neurological defects like microcephaly with mental retardation, seizure disorder, and delayed milestones had a negative impact on final vision. This factor emphasizes the additional component of cortical visual impairment in addition to visual impairment caused by cataract. Here, visual stimulation and appropriate visual rehabilitation measures take a bigger role than a well-performed cataract surgery.

Postoperatively two eyes had aphakic glaucoma and four eyes developed posterior capsular opacification, both of which were managed surgically. Ten eyes had transient corneal edema which resolved spontaneously, five eyes had exaggerated anterior chamber reaction which was managed medically.

Despite many eyes having multiple associated ocular and systemic factors, we were surprised to find 44.5% eyes having vision better than 20/60. This was in contrast to a previous study,^[5] where they reported only 15% eyes to have vision better than 20/80. This made us to retrospectively go back and analyze the factors responsible for the good visual outcome in our study.

1. 60% of infants were less than 6 months of age, with the mean age of surgery being 6.2 months. Age has always been known as an important prognostic factor, with early detection and early surgery being associated with better outcomes postcataract surgery.^[26]
2. This study being undertaken in a tertiary eye care center has higher chances of early referrals from pediatricians and neonatologists. All the infants selected had bilateral cataract which does affect vision earlier as compared to monocular cataract making detection easy for parents and pediatricians. As seen in previous studies,^[26] bilaterality itself is a positive factor for final visual outcome as compared to a child with monocular cataract
3. 41% of eyes had total cataract, which again aided earlier diagnosis leading to early referral and early surgery. 32% eyes had zonular cataract which as such is known to have a good visual outcome. Further, exclusion of children who were noncompliant with follow-up or amblyopia management adds up to better outcome results
4. Normally the fitness for anesthesia and surgical procedure becomes an important factor which determines timing of surgery which is so crucial for optimum visual outcome. In our study, multidisciplinary approach with super specialists reduced the wait time between diagnosis and surgery.

In such children, postcataract surgery, parents tend to lose on us with follow-up as the other systemic rehabilitation takes prominence. Thorough counseling of parents that post-surgical vision rehabilitation and amblyopia management is as important as cardiac and neurological management is an integral part of treatment protocol which on a long-term basis helps us in restoring a better vision.

Conclusion

Based on our data, we conclude that the morphology of cataract, microphthalmos, iris hypoplasia, nystagmus, optic nerve involvement, and neurological defects display a statistical correlation of rubella cataracts with poor visual prognosis postcataract surgery. Pigmentary retinopathy, cloudy cornea, cardiac and hearing anomalies have minimal influence on final visual outcome postcataract surgery.

Ophthalmologists have always had a pessimistic mindset about rubella cataracts as it is considered to be congenital and multisystem pathology. Through this study, we would like to stress that despite many factors like microphthalmos or neurological anomalies which are beyond our control, if we proceed with a well-defined treatment protocol with respect to time of surgery, postsurgical visual rehabilitation, appropriate and timely management of complications without neglecting ocular and systemic comorbidities and with patient and parent compliance, we can always hope to get best VA in child with rubella cataract for many decades to live.

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Conflicts of interest

There are no conflicts of interest.

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