RESEARCH PAPER

Lack of Screening Underlies Most Stage-5 Retinopathy of Prematurity among Cases Presenting to a Tertiary Eye Center in India

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Objective: To study the barriers to effective screening, early detection and treatment of Retinopathy of Prematurity leading to advanced disease.

Design: Cross-sectional study

Setting: Tertiary eye care hospital in northern India.

Participants: 115 babies with bilateral stage 5 ROP identified amongst 354 preterm infants examined over a one year period.

Methods: Information regarding gestational age, birthweight, duration of stay in nursery, duration of supplemental oxygen therapy and treatment details were obtained from discharge summary when available, and by interviewing carers.28 stage 5 ROP eyes underwent pars plana lensectomy and vitrectomy.

Results: Among the 354 infants (708 eyes) examined, 115 had stage 5 ROP in both eyes. The mean post conceptional age (PCA) at first visit to an ophthalmologist was 54.6 (7.6) weeks (Median 52.9 ± 4.2). The mean overall delay in first examination for Retinopathy of Prematurity was 24.7 (3.9) weeks. Most common risk factor was oxygen therapy in 103 babies (89.6%). 109 (89.8%) babies had never been screened for ROP; four babies fell outside the NNF guidelines (i.e. they had a birth weight of 1750 gms or more and were born at 34 weeks gestational age or more). Another important finding is that only 4.3% of babies were given the correct diagnosis. While 99 babies (86.1%) were referred by ophthalmologists, only 10 babies (8.7%) were referred by pediatricians. A large number were from the capital city of Delhi (21 babies, 18.2%). 28 stage 5 ROP eyes (12.1%) underwent surgery, and at 6 months follow up, only 20 operated eyes had visible attached posterior pole. 210 (91.3%) stage 5 eyes were irreversibly blind.

Conclusion: ROP is an increasingly important cause of leucocoria. There were notable gaps in timely ROP screening, referral and treatment and much needs to be done to improve awareness amongst ophthalmologists about ROP. Measures are needed to improve the coverage of initiatives for the detection and timely treatment of sight threatening ROP in India as well as improving neonatal care to reduce sight threatening ROP in bigger, more mature infants.

Keywords*: Childhood blindness, Screening, Outcome, Treatment delay.*

Retinopathy of Prematurity (ROP) is emerging as a major cause of childhood blindness in India. The highest number of live births (37.1 million, 28%) and largest number of preterm births (4.95 million, 33%), are reported in the South Asia region; which predisposes an estimated 79,600 babies to have high risk of developing ROP annually [1]. The uncontrolled growth of Neonatal Intensive Care Units (NICU) with poor neonatal care/untrained personnel,and the fact that not all the neonatal care units have programmes for the detection and treatment of ROP, is leading to larger numbers of preterm babies developing severe ROP [2,3]. Concentration of ophthalmologists in large cities, lack of ROP orientation in residency programs, poor financial support for equipment and salaries are important barriers in many developing countries [4].

The South Asia region primarily includes India, where despite well-established ROP screening protocols [5],the lack of awareness among all stakeholders and ineffective ROP screening programs commonly leads to advanced stage 5 ROP referral across tertiary eye care hospitals. The current US guidelines,which many centres follow, tend to overlook possibility of ROP in relatively larger and mature babies, which is not uncommon in developing countries like India [6]. The screening guidelines by National Neonatology Forum (NNF) advocate screening of all preterm neonates who are born <34 weeks gestation and or <1750g birthweight; as well as in babies 34-36 weeks gestation or 1750-2000g birthweight if they have risk factors for ROP.They advise all babies should be screened within 4 weeks of life or as early as 2-3 weeks in babies <28 wks gestation age and <1200g birthweight for early detection of aggressive posterior ROP [7]. The study presents insights into the alarming increase in stage 5 ROP in India and the underlying reasons.

METHODS

A prospective study was designed to determine the barriers leading to advanced stages of ROP. We included all babies referred and diagnosed with bilateral stage 5 ROP at our tertiary eyecare hospital over a period of one year (2012). Information regarding gestational age, birth weight, type of gestation, duration of NICU care, duration of supplemental oxygen therapy, and type of treatment received in NICU was obtained by interviews with caregivers. Previous treatment records, discharge summary and referral letters were also reviewed, whenever available. The study adopted standard International screening guidelines which recommend screening babies <32 weeks gestation age and <1500g birthweight or higher if baby was at high risk to develop ROP [5].The delay in screening time (lag period) was calculated by subtracting the recommended time for first ROP screening (within 4 weeks after birth) from chronological age at first visit to ophthalmologist.

All stage 5 babies underwent detailed ocular examination with indirect ophthalmoscopy, Retcam (Clarity Systems, USA), and B-scan ultrasound (to study retinal funnel status). Babies with mainly open-open funnel configuration onultrasound underwent vitreoretinal surgery under general anaesthesia after informed consent from parents. Operated babies were followed up at one week, one month and every three months. Successful surgical outcome was defined as attached posterior pole maintained at 6 months follow up.

RESULTS

354 consecutive new referrals who attended the ROP clinic at a tertiary eye care centre in northern India were examined. Of these,115 babies (230 eyes, 32.48%) were diagnosed with bilateral stage 5 ROP at presentation and were included in the study. All these stage 5 babies were outborn babies referred from elsewhere. The most common risk factor for ROP was prolonged oxygen therapy in 103 babies (89.6%) (***Table* I**).

While 99 babies (86.1%) were referred by ophthalmologists, only 10 babies (8.7%) were referred by pediatricians and 6 babies were brought by parents for second expert opinion. The referral letters mentioned diagnosis for only 126 eyes (54.7%), with correctly diagnosed stage 5 ROP in only 10 eyes (4.3%), 'possibly ROP' diagnosis in 8 eyes (3.4%), and most were referred for leukocoria (***Table* II**). Information was provided by parents for 86 babies (74.7%) and grandparents for 17 babies (14.7%).

A large number of these 115 cases were from the state of Delhi (21 babies, 18.2%), Haryana (26 babies, 22.6%), Uttar Pradesh (22 babies, 19.1%), Rajasthan (13 babies, 11.3%) and Bihar (10 babies, 8.7%).Seventy nine cases (68.9%) were referred from rural areas. It is notable that 109 babies (89.8%) were never screened for ROP previously.The mean (SD) gestational age was 29.1 (2.3) weeks (25-36 weeks) and mean (SD) birthweight was 1323.1 (450.9 g) (600-2800g). Seven babies (6%) were born between 34-36 weeks of gestation and 8 babies (6.9%) had birthweight between 1750-2000 g. Five preterm babies had birthweight more than 2000 g. All these relatively mature and larger babies had history of NICU admission and had received oxygen therapy in postnatal period, and were beyond the NNF guidelines primary criteria. The majority were males (58.2%) and singleton births (74.8%).The chronological age at presentation to our centre ranged from 22 to 104 weeks

TABLE I SYSTEMIC DISEASES AND RISK FACTORS IN STAGE 5 ROP BABIES (*N*=115)

	No. (%)
**Risk factors*	
Supplemental Oxygen therapy	103 (89.6)
Sepsis	51 (44.3)
Respiratory distress syndrome	22 (19.1)
Blood transfusion	25 (21.7)
#*Risk factors*	
Apnea	26 (22.6)
Asphyxia	06 (5.2)
Jaundice	42 (36.5)
Intraventricular hemorrhage	13 (11.3)
Patent ductus arteriosus	02 (1.7)

**known to be associated with increased risk of ROP;* #*likely to be associated with increased risk of ROP.*

TABLE II OCULAR DIAGNOSIS AS PER MEDICAL RECORDS BY REFERRING PHYSICIAN (*N*=230 EYES)

Diagnosis	*No. (%)*
No ocular diagnosis mentioned	104 (45.2)
Stage 5 ROP	10 (4.3)
Leukocoria	78 (33.9)
Congenital cataract	32 (13.9)
Retinoblastoma	20 (8.7)
Total retinal detachment	14 (6)
Possibly ROP	8 (3.5)
PHPV	4 (1.7)
Squint/nystagmus	22 (9.6)
Corneal opacity	16 (6.9)

TABLE III RETINAL FUNNEL CONFIGURATION ON B-SCAN ULTRASONOGRAPHY AND SURGICAL OUTCOMES

Retinal funnel (anterior-posterior)	*No. of eyes (N=230)*	*Surgery done (N=28)*	*Anatomical Success*
Closed-Closed	26	-	-
Open-Closed	175	2	0
Open-Open	22	22	17
Indeterminate	7	4	3

(Mean (SD) 43.2 (11.3) weeks; Median 40.2 weeks). The mean (SD) PCA at first visit to an ophthalmologist overall was 54.6 (7.6) weeks (Median 52.9 (4.2) weeks). The mean (SD) lag period (or delay) in ROP examination overall was 24.7 (3.9) weeks.

One hundred and ten babies (96.5%) had not received any form of ophthalmic treatment before reaching our centre.Three babies had undergone vitrectomy and two had received intravitreal Bevacizumab. 115 babies had bilateral stage 5 ROP with associated posterior synechiae (156 eyes, 67.8%), corneal opacity (12 eyes), and buphthalmos (4 babies).

Primarily based on the open-open configuration on B-scan ultrasonography, 28 eyes (out of 230 stage 5 eyes) underwent pars plana lensectomy and vitrectomy, and at last follow up of 6 months, only 20 operated eyes had visible attached posterior poles, and might possibly have some vision **(*Table* III**); 210 stage 5 eyes (91.3%) were irreversibly blind.

DISCUSSION

ROP has huge social and economic implications on the society and it is estimated that a blind child due to ROP will lead to a burden of over US$ 50,000 in his lifetime, which could be avoided by a laser treatment intervention costing under US$ 100 [8]. Estimates of blindness from ROP for the year 2010 suggest that 20,000 preterm infants become blind globally every year, 2,200 of which are in the south Asia region [1]. Stage 5 ROP serves as an important indicator of poor quality of neonatal care (especially in larger babies), lack of timely screening and treatment services leading to blindness which was potentially avoidable.

An alarming finding was that 115 babies with stage 5 ROP presented to one tertiary facility over a one year period, and the vast majority (109 babies) had never been screened for ROP. Similar findings have been reported in a study of 66 cases of stage 5 ROP in India in which Sanghi, *et al*. [3] reported that 57 infants (86.4%) were not screened for ROP. In another study, Patwardhan, *et al*. [9] interviewed pediatricians from different part of India, and although all respondents were aware of the ophthalmic complications of premature birth including ROP, only 58% pediatricians always referred premature infants for ROP screening. In a study of the knowledge, attitudes and practices of 83 pediatricians, Sathiamohanraj, *et al*. [10] found that only 54 (65.1%) were aware of ROP, 33 (39.8%) knew that ROP is preventable, 34 (41%) did not know which part of the eye is affected in ROP, and 38 (45.8%) did not know when ROP screening should start. Only 43 (51.8%) pediatricians were sure that ROP is treatable. All these findings suggest that much needs to be done in India to increase awareness about ROP amongst pediatricians who care for preterm infants, and the need for screening and timely treatment.

In this study, several infants fell outside both primary NNF screening criteria, which suggest that the criteria either need to be reviewed and widened, or greater clarity is required concerning which sickness criteria should be applied. In our study, larger, more mature babies were also given supplemental oxygen, and the number of days in oxygen could be an easily measurable indicator of the need for ROP screening among more mature infants.

In almost half of the babies in this study a diagnosis was not made by the referring clinician. When a diagnosis was mentioned, in one third the white pupils were thought to be due to congenital cataract, retinoblastoma, PHPV and total detachment, with a few mentioning possible ROP. This suggests that much needs to be done to improve awareness among ophthalmologists that end-stage ROP can also be a cause of leucocoria in infants and young children born preterm, together with the need for urgent referral to a tertiary centre with expertise in the surgical management of end-stage ROP.

Almost one in five cases of Stage 5 ROP was referred from within the capital city, Delhi, indicating a lack of screening and or treatment which needs to be addressed. The study also includes seven babies which were from outside India, but referred for stage 5 management, and two such babies did undergo successful surgery. The fact that neighbouring countries are referring cases, stresses the fact that similar ROP blindness issues might be widespread in the subcontinent.

It is well-known that surgical results in stage 5 ROP are poor and since the disease is bilateral, it often results in total blindness [11,12]. Few selected cases are operable (many have secondary ocular complications) and there are few surgeons with advanced vitreoretinal surgical setups and associated pediatrics/anaesthesia support systems. Though few babies with open retinal funnels could be operated in our series, very few operated

WHAT IS ALREADY KNOWN?

- Stage 5 end-stage ROP is an important cause of childhood blindness and is indicative of poor ROP services.

WHAT THIS STUDY ADDS?

- The study highlights the gaps in screening, referral and treatment which are leading to an alarming increase in end-stage blinding ROP in India

eyes had visible attached posterior pole, which also does not assure good vision. Eventually >90% eyes were still irreversibly blind, which could be potentially avoided had they been screened for ROP.

The study is limited by the fact that it represents the spectrum of patients visiting a single referral tertiary eyecare hospital, and may not be representative of the ROP patient profile presenting to many other smaller centres, and also may not be representative of other major regions across the country.

Zepeda-Romero, *et al*. [4] have reported similar issues in Mexico and suggest more needs to be done to improve the coverage of programs. They report barriers to the expansion of programs including, the concentration of ophthalmologists in large cities, and residency programs mostly do not include training in ROP thereby junior ophthalmologists do not develop skills or interest in ROP. Getting financial support for equipment and salaries is also challenging. Thus, most programs often run on a voluntary basis, with lack of continuity, or neonatologists hire ophthalmologists to run programs to reduce the risk of medicolegal action.They suggest it would be best to develop more regional ROP centres of excellence, provide local leadership for program development and to ensure quality control.

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